Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

One-step Construction of Complex Polyheterocycles via a Sequential Post-GBB Cyclization/Spiro Ring Expansion Triggered by a [1,5]-Hydride Shift

Sandip Gangadhar Balwe, Yeon Tae Jeong*

Department of Image Science and Engineering, Pukyong National University, Busan 608-737, Republic of Korea, Corresponding author: Tel.: +82-51-629-6411; fax: +82-51-629- 6408

Table of Contents

General Information

Chemicals were purchased from Aldrich and Alfa Aesar Chemical Companies and used without further purification. NMR spectra were recorded in parts per million (ppm) in DMSO-d6 on a Jeol JNM ECP 600 NMR instrument using TMS as internal standard. Standard abbreviations were used to denote signal multiplicities (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). HRMS were obtained by EI on a double-focusing mass analyzer, ESI (positive ion mode) on TOF mass analyzer. All melting points were determined using open capillaries on an Electrothermal-9100 (Japan) instrument and are uncorrected.

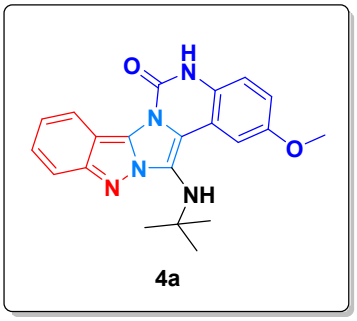
Experimental procedure

General procedure for the synthesis of the Synthesis of amino-indazolo[3',2':2,3]imidazo[1,5-*c*]quinazolin-6(5*H*)-ones.

To a mixture of 3-amino-1*H*-indazoles (**1a**, 1 mmol), isatin (**2a**, 1 mmol) and *tert*-butyl isocynide (**3a**, 1 mmol), in 3 ml of ethanol was added *p*-TSA (40 mol %) and the reaction mixture was stirred at 80 ºC for 6-8 h. The progress of the reaction was monitored by TLC. After completion of the reaction, solid products was filtered under vacuum, air dried, to obtain the analytically pure products. The compounds **4a-4x** were also synthesized by adopting this procedure.

Characterization Data of the compounds

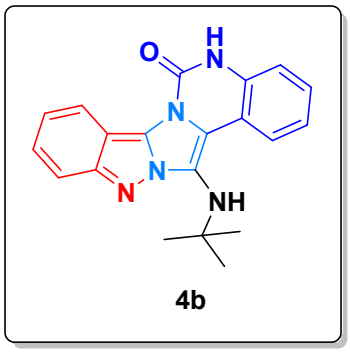
14-(*tert*-butylamino)-2-methoxyindazolo[3',2':2,3]imidazo[1,5-*c*]quinazolin-6(5*H*)-one (4a)



4a

Yield: 87 % (326.4 mg); off White solid; Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.47 (s, 1H), 8.36 (d, J = 8.3 Hz, 1H), 8.20 (d, J = 2.8 Hz, 1H), 7.61 (d, J = 8.7 Hz, 1H), 7.33 – 7.29 (m, 1H), 7.19 (d, J = 8.8 Hz, 1H), 7.06 – 7.01 (m, 2H), 4.99 (s, 1H), 3.83 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 154.72, 151.47, 143.88, 128.16, 127.38, 125.77, 121.48, 121.12, 120.75, 117.88, 116.95, 116.71, 115.45, 113.38, 106.56, 105.78, 55.48, 55.45, 30.60.; HRMS (ESI, m/z): calcd for $C_{21}H_{21}N_5O_2$ ($M+H^+$) 375.1695, found: 375.1691.

14-(*tert*-butylamino)indazolo[3',2':2,3]imidazo[1,5-*c*]quinazolin-6(5*H*)-one (4b)

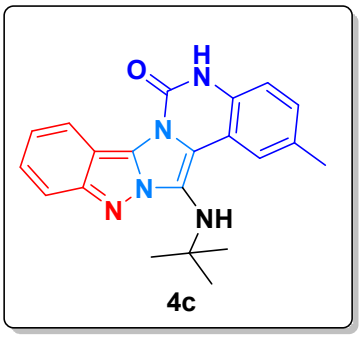


4b

Yield: 92 % (317.6 mg); Yellow solid; Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.59 (s, 1H), 8.66 (d, J = 7.8 Hz, 1H), 8.36 (d, J = 8.3 Hz, 1H), 7.62 (d, J = 8.7 Hz, 1H), 7.41 (t, J = 8.3 Hz, 1H), 7.35 – 7.29 (m, 1H), 7.27 (t, J = 7.7 Hz, 2H), 7.07 – 7.00 (m, 1H), 4.95 (s, 1H), 1.33 (s, 9H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 151.40, 144.09, 134.38, 128.99, 127.28, 125.73, 123.56,

122.80, 121.40, 121.18, 120.82, 117.90, 115.69, 115.49, 112.78, 105.80, 55.77, 30.49.; HRMS (ESI, m/z): calcd for $C_{20}H_{19}N_5O$ ($M+H^+$) 345.1590, found: 345.1587.

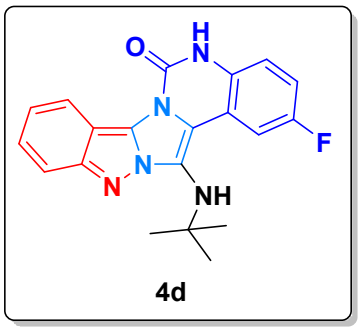
14-(*tert*-butylamino)-2-methylindazolo[3',2':2,3]imidazo[1,5-*c*]quinazolin-6(5*H*)-one (4c)



4c

Yield: 85 % (307 mg); Pink solid; Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.50 (s, 1H), 8.47 (s, 1H), 8.36 (d, J = 8.3 Hz, 1H), 7.61 (d, J = 8.7 Hz, 1H), 7.35 – 7.27 (m, 1H), 7.21 (dd, J = 8.3, 1.5 Hz, 1H), 7.14 (d, J = 8.2 Hz, 1H), 7.07 – 6.99 (m, 1H), 4.88 (s, 1H), 2.36 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 151.41, 144.05, 132.12, 131.74, 129.77, 127.27, 125.69, 123.45, 121.41, 121.16, 120.61, 117.86, 115.51, 115.46, 112.58, 105.83, 55.77, 30.51, 20.72.; HRMS (ESI, m/z): calcd for $C_{21}H_{21}N_5O$ ($M+H^+$) 359.1746, found: 359.1749.

14-(*tert*-butylamino)-2-fluoroindazolo[3',2':2,3]imidazo[1,5-*c*]quinazolin-6(5*H*)-one (4d)

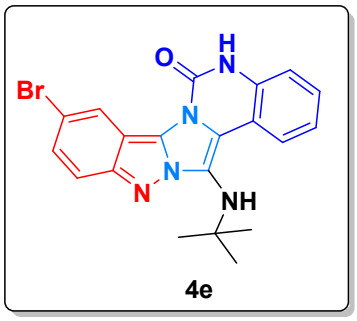


4d

Yield: 83 % (302 mg); Brown solid; Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.64 (s, 1H), 8.42 – 8.31 (m, 2H), 7.62 (d, J = 8.7 Hz, 1H), 7.35 – 7.25 (m, 3H), 7.07 – 6.98 (m, 1H), 5.07 (s, 1H), 1.33 (s, 9H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 158.23, 156.65, 151.59, 143.86, 131.02, 127.52, 125.95, 121.45, 121.40, 120.34, 120.32, 118.02, 117.48, 117.42, 116.35, 116.19,

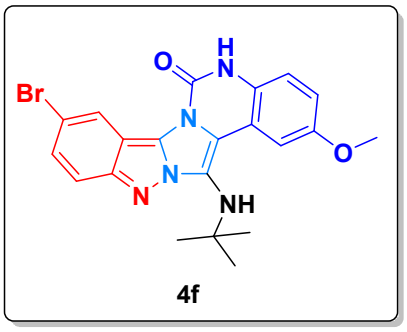
115.54, 133.96, 113.89, 109.19, 109.02, 105.66, 55.82, 30.48.; ^{19}F NMR (565 MHz, DMSO-d_6) δ -119.14 (s, 1F); HRMS (ESI, m/z): calcd for $C_{20}H_{18}FN_5O$ ($M+H^+$) 363.1495, found: 363.1498.

9-bromo-14-(*tert*-butylamino)indazolo[3',2':2,3]imidazo[1,5-*c*]quinazolin-6(5*H*)-one (4e)



Yield: 87 % (368.48 mg); Off White solid; Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.65 (s, 1H), 8.62 (d, J = 8.0 Hz, 1H), 8.46 (s, 1H), 7.58 (d, J = 9.1 Hz, 1H), 7.43 – 7.34 (m, 2H), 7.25 (t, J = 7.3 Hz, 2H), 4.88 (s, 1H), 1.30 (s, 9H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 149.59, 143.81, 134.22, 128.97, 128.29, 126.40, 123.41, 122.88, 122.66, 121.54, 120.67, 117.45, 115.62, 112.40, 109.42, 106.77, 55.47, 30.25.; HRMS (ESI, m/z): calcd for $C_{20}H_{18}BrN_5O$ ($M+H^+$) 423.0695, found: 423.0690.

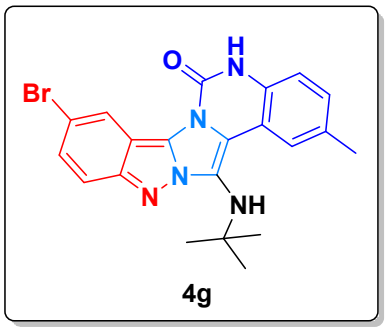
9-bromo-14-(*tert*-butylamino)-2-methoxyindazolo[3',2':2,3]imidazo[1,5-*c*]quinazolin-6(5*H*)-one (4f)



Yield: 81 % (367 mg); Brown solid; Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.56 (s, 1H), 8.48 (s, 1H), 8.18 (s, 1H), 7.60 (d, J = 9.1 Hz, 1H), 7.39 (d, J = 9.1 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 7.10– 7.0 (m, 1H), 5.00 (s, 1H), 3.83 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (150 MHz,

DMSO-d_6) δ 154.62, 149.46, 143.33, 127.97, 127.90, 126.30, 122.74, 121.22, 120.38, 117.10, 116.56, 116.49, 112.82, 109.08, 106.87, 106.52, 55.21, 54.87, 30.09.; HRMS (ESI, m/z): calcd for $C_{21}H_{20}BrN_5O_2$ ($M+H^+$) 453.0800, found: 453.0804.

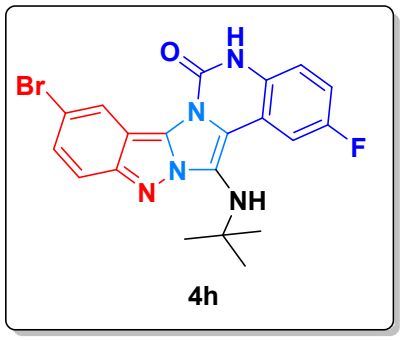
9-bromo-14-(tert-butylamino)-2-methylindazolo[3',2':2,3]imidazo[1,5-*c*]quinazolin-6(5*H*)-one (4g)



4g

Yield: 86 % (375.6 mg); Off white solid; Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.39 (s, 1H), 8.59–8.38 (m, 2H), 7.58 (s, 1H), 7.38 (s, 1H), 7.28–7.12 (m, 2H), 4.71 (s, 1H), 2.38 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 149.45, 143.62, 131.86, 131.56, 129.59, 128.04, 126.25, 123.18, 122.76, 121.38, 120.37, 117.25, 115.33, 112.10, 109.18, 106.64, 55.27, 30.13, 20.15.; HRMS (ESI, m/z): calcd for $C_{21}H_{20}BrN_5O$ ($M+H^+$) 437.0851, found: 437.0855.

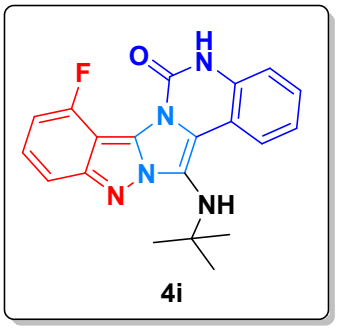
9-bromo-14-(*tert*-butylamino)-2-fluoroindazolo[3',2':2,3]imidazo[1,5-*c*]quinazolin-6(5*H*)-one (4h)



4h

Yield: 84 % (371 mg); White solid; Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.68 (s, 1H), 8.44 (s, 1H), 8.32 (d, J = 9.7 Hz, 1H), 7.58 (d, J = 9.1 Hz, 1H), 7.37 (d, J = 9.1 Hz, 1H), 7.32 – 7.23 (m, 2H), 4.98 (s, 1H), 1.31 (s, 9H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 158.15, 156.57, 149.74, 143.54, 130.83, 128.46, 126.59, 122.90, 121.22, 117.40, 116.21, 109.51, 109.09, 108.91, 106.61, 55.49, 30.22.; ^{19}F NMR (565 MHz, DMSO-d_6) δ -118.91 (s, 1F) ; HRMS (ESI, m/z): calcd for $C_{20}H_{17}BrFN_5O$ ($M+H^+$) 441.0601, found: 441.0605.

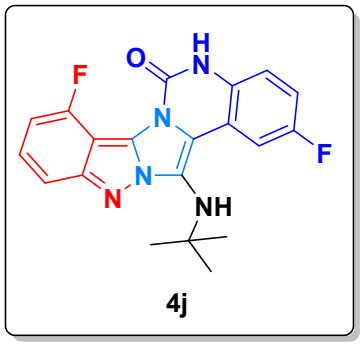
14-(*tert*-butylamino)-8-fluoroindazolo[3',2':2,3]imidazo[1,5-*c*]quinazolin-6(5*H*)-one (4i)



4i

Yield: 87 % (316 mg); Pink solid; Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.49 (s, 1H), 8.70 (dd, J = 8.3, 1.3 Hz, 1H), 7.46 (d, J = 8.6 Hz, 1H), 7.43 – 7.39 (m, 1H), 7.31 – 7.23 (m, 3H), 6.81–6.74 (m, 1H), 4.94 (s, 1H), 1.31 (s, 9H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 154.62, 153.46, 153.43, 152.92, 142.85, 134.17, 128.94, 125.32, 124.27, 123.48, 122.27, 121.79, 120.41, 115.14, 112.26, 111.71, 102.65, 102.51, 96.67, 55.60, 30.26.; ^{19}F NMR (565 MHz, DMSO-d_6) δ -107.24 (s, 1F); HRMS (ESI, m/z): calcd for $C_{20}H_{18}FN_5O$ ($M+H^+$) 363.1495, found: 363.1492.

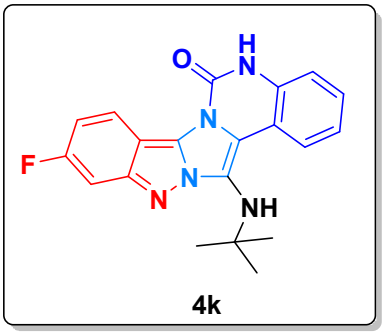
14-(*tert*-butylamino)-2,8-difluoroindazolo[3',2':2,3]imidazo[1,5-*c*]quinazolin-6(5*H*)-one (4j)



4j

Yield: 82 % (314 mg); Pink solid; Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.54 (s, 1H), 8.44–8.40 (m, 1H), 7.47 (d, J = 8.6 Hz, 1H), 7.34 – 7.25 (m, 3H), 6.81–6.76 (m, 1H), 5.08 (s, 1H), 1.32 (s, 9H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 157.91, 156.34, 154.63, 153.58, 152.92, 142.62, 130.81, 125.56, 124.50, 120.96, 116.92, 116.35, 116.19, 113.36, 111.76, 109.15, 108.98, 102.75, 102.61, 96.57, 55.66, 30.25.; ^{19}F NMR (565 MHz, DMSO-d_6) δ -107.10 (s, 1F), -119.40 (s, 1F); HRMS (ESI, m/z): calcd for $C_{20}H_{17}F_2N_5O$ (M+H$^+$) 381.1401, found: 381.1404.

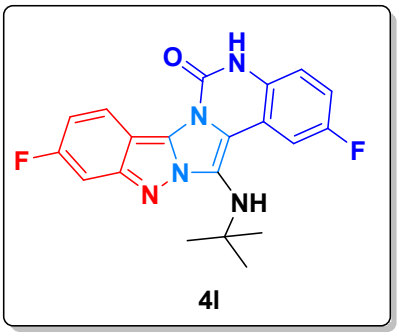
14-(*tert*-butylamino)-10-fluoroindazolo[3',2':2,3]imidazo[1,5-*c*]quinazolin-6(5*H*)-one (4k)



4k

Yield: 88 % (320.2 mg); Pale yellow solid; Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.40 (s, 1H), 8.64 (d, J = 7.9 Hz, 1H), 8.39 (dd, J = 8.8, 5.9 Hz, 1H), 7.46 – 7.37 (m, 1H), 7.33 – 7.22 (m, 3H), 6.95 – 6.83 (m, 1H), 4.67 (s, 1H), 1.36 (s, 9H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 161.71, 160.12, 151.06, 150.97, 143.67, 134.00, 128.53, 127.20, 123.04, 122.41, 120.70, 120.57, 115.39, 112.40, 107.83, 107.65, 103.00, 98.60, 98.44, 55.23, 30.11.; ^{19}F NMR (565 MHz, DMSO-d_6) δ -114.70 (s, 1F); HRMS (ESI, m/z): calcd for $C_{20}H_{18}FN_5O$ (M+H$^+$) 363.1495, found: 363.1491.

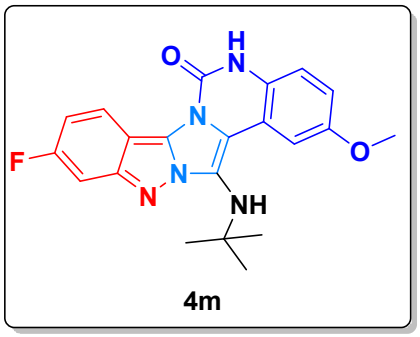
14-(*tert*-butylamino)-2,10-difluoroindazolo[3',2':2,3]imidazo[1,5-*c*]quinazolin-6(5*H*)-one (4l)



4l

Yield: 85 % (324.3 mg); Off white solid; Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.55 (s, 1H), 8.39 – 8.30 (m, 2H), 7.34 – 7.24 (m, 3H), 6.94–6.85 (m, 1H), 4.89 (s, 1H), 1.34 (s, 9H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 161.82, 160.22, 158.03, 156.45, 151.21, 143.42, 130.61, 127.42, 123.06, 121.26, 119.73, 117.14, 115.85, 115.69, 113.53, 108.83, 108.66, 108.00, 107.82, 102.86, 98.65, 98.49, 55.29, 30.09.; ^{19}F NMR (565 MHz, DMSO-d_6) δ -114.35 (s, 1F), -119.00 (s, 1F); HRMS (ESI, m/z): calcd for $C_{20}H_{17}F_2N_5O$ (M+H$^+$) 381.1401, found: 381.1406.

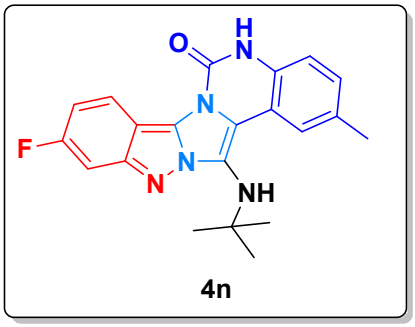
14-(*tert*-butylamino)-10-fluoro-2-methoxyindazolo[3',2':2,3]imidazo[1,5-*c*]quinazolin-6(5*H*)-one (4m)



4m

Yield: 84 % (331 mg); White solid; Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.38 (s, 1H), 8.37 (dd, J = 8.9, 6.0 Hz, 1H), 8.18 (s, 1H), 7.30 (d, J = 9.0 Hz, 1H), 7.19 (d, J = 8.9 Hz, 1H), 7.02 (dd, J = 8.8, 2.7 Hz, 1H), 6.89 (t, J = 9.2 Hz, 1H), 4.81 (s, 1H), 3.84 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 161.75, 160.16, 154.65, 151.09, 143.48, 127.85, 127.29, 123.07, 120.58, 116.61, 116.35, 113.02, 107.79, 107.61, 106.72, 102.98, 98.57, 98.41, 55.25, 54.99, 30.20.; ^{19}F NMR (565 MHz, DMSO-d_6) δ -114.65 (s, 1F); HRMS (ESI, m/z): calcd for $C_{21}H_{20}FN_5O_2$ (M+H$^+$) 393.1601, found: 393.1604.

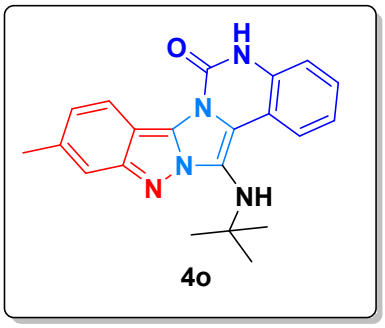
14-(*tert*-butylamino)-10-fluoro-2-methylindazolo[3',2':2,3]imidazo[1,5-*c*]quinazolin-6(5*H*)-one (4n)



4n

Yield: 87 % (329 mg); White solid; Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.43 (s, 1H), 8.45 (s, 1H), 8.41 – 8.33 (m, 1H), 7.35–7.12 (m, 3H), 6.89 (t, J = 9.0 Hz, 1H), 4.75 (s, 1H), 2.37 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 163.90, 158.91, 150.46, 149.44, 147.99, 134.57, 129.07, 128.94, 126.73, 124.20, 122.40, 121.27, 117.46, 117.28, 116.73, 115.52, 113.41, 111.90, 110.78, 106.00, 55.36, 30.13.; ^{19}F NMR (565 MHz, DMSO-d_6) δ -114.76 (s, 1F); HRMS (ESI, m/z): calcd for $C_{21}H_{20}FN_5O$ ($M+H^+$) 377.1652, found: 377.1657.

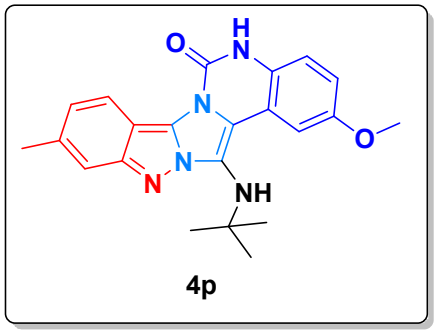
14-(*tert*-butylamino)-10-methylindazolo[3',2':2,3]imidazo[1,5-*c*]quinazolin-6(5*H*)-one (4o)



4o

Yield: 85 % (306.2 mg); White solid; Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.28 (s, 1H), 8.65 (d, J = 6.9 Hz, 1H), 8.14 (s, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 6.5 Hz, 1H), 7.34 – 7.22 (m, 2H), 7.16 (d, J = 7.5 Hz, 1H), 4.61 (s, 1H), 2.44 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 150.16, 143.66, 134.05, 128.39, 127.76, 126.54, 126.09, 123.12, 122.28, 120.52, 119.32, 115.29, 115.00, 112.49, 105.49, 55.18, 30.14, 20.84.; HRMS (ESI, m/z): calcd for $C_{21}H_{21}N_5O$ ($M+H^+$) 359.1746, found: 359.1741.

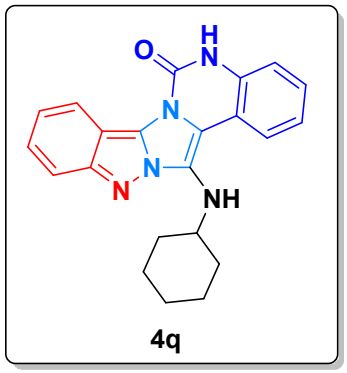
14-(*tert*-butylamino)-2-methoxy-10-methylindazolo[3',2':2,3]imidazo[1,5-*c*]quinazolin-6(5*H*)-one (4p)



4p

Yield: 82 % (319.2 mg); White solid; Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.16 (s, 1H), 8.22 (d, J = 2.8 Hz, 1H), 8.15 (s, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.22 (d, J = 8.9 Hz, 1H), 7.16 (dd, J = 8.8, 1.5 Hz, 1H), 7.03 (dd, J = 8.9, 2.8 Hz, 1H), 4.69 (s, 1H), 3.85 (s, 3H), 2.44 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 154.56, 150.21, 143.48, 127.91, 127.78, 126.63, 126.04, 120.55, 120.41, 119.39, 116.50, 116.23, 114.96, 113.12, 106.75, 105.46, 55.25, 54.92, 30.23, 20.83.; HRMS (ESI, m/z): calcd for $C_{22}H_{23}N_5O_2$ ($M+H^+$) 389.1852, found: 389.1857.

14-(cyclohexylamino)indazolo[3',2':2,3]imidazo[1,5-*c*]quinazolin-6(5*H*)-one (4q)

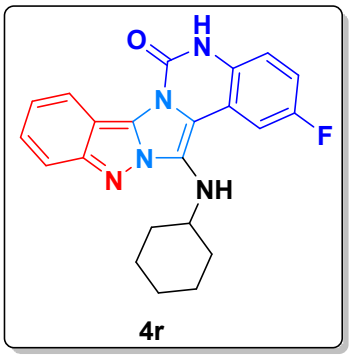


4q

Yield: 89 % (330 mg); Off white solid; Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.27 (s, 1H), 8.43 (d, J = 7.9 Hz, 1H), 8.37 (d, J = 8.3 Hz, 1H), 7.63 (d, J = 8.7 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 7.34 – 7.30 (m, 1H), 7.29 – 7.25 (m, 2H), 7.06 – 7.01 (m, 1H), 4.96 (d, J = 4.8 Hz, 1H), 3.74 – 3.66 (m, 1H), 1.98 – 1.91 (m, 2H), 1.78 – 1.71 (m, 2H), 1.60 – 1.53 (m, 1H), 1.48 – 1.40 (m, 2H), 1.32 – 1.20 (m, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 152.27, 144.65, 134.56, 129.00, 127.70, 126.37, 123.63, 123.47, 122.60, 121.89, 118.46, 118.03, 116.13, 115.93, 113.52,

106.25, 55.02, 33.80, 26.02, 24.93.; HRMS (ESI, m/z): calcd for $C_{22}H_{21}N_5O$ (M+H$^+$) 371.1746, found: 371.1742.

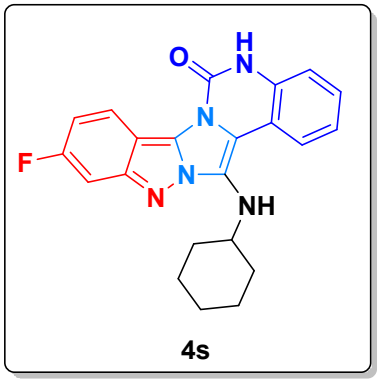
14-(cyclohexylamino)-2-fluoroindazolo[3',2':2,3]imidazo[1,5-*c*]quinazolin-6(5*H*)-one (4r)



4r

Yield: 86 % (335.7 mg); Off White solid; Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.53 (s, 1H), 8.34 (d, J = 8.3 Hz, 1H), 8.17 (d, J = 9.7 Hz, 1H), 7.63 (d, J = 8.7 Hz, 1H), 7.34 – 7.30 (m, 1H), 7.26 – 7.22 (m, 2H), 7.05 – 7.01 (m, 1H), 5.39 (d, J = 5.9 Hz, 1H), 3.77 – 3.66 (m, 1H), 1.97 – 1.87 (m, 2H), 1.75 – 1.67 (m, 2H), 1.60 – 1.50 (m, 1H), 1.44 – 1.35 (m, 2H), 1.29 – 1.14 (m, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 158.58, 157.00, 151.97, 143.91, 130.61, 127.45, 126.07, 122.80, 121.47, 118.03, 117.26, 116.16, 115.58, 115.43, 114.22, 108.71, 108.53, 105.58, 54.26, 33.36, 25.48, 24.43.; ^{19}F NMR (565 MHz, DMSO-d_6) δ -118.92 (s, 1F); HRMS (ESI, m/z): calcd for $C_{22}H_{20}FN_5O$ (M+H$^+$) 389.1652, found: 389.1656.

14-(cyclohexylamino)-10-fluoroindazolo[3',2':2,3]imidazo[1,5-*c*]quinazolin-6(5*H*)-one (4s)

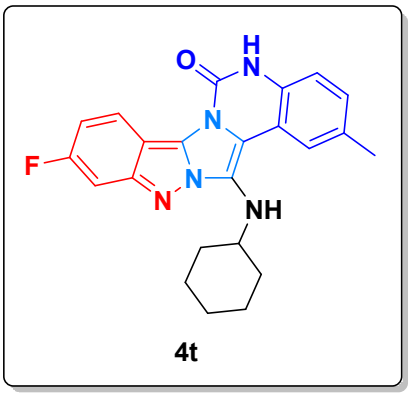


4s

Yield: 84 % (327 mg); Pink solid; Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.56 (s, 1H), 8.41 (d, J = 7.7 Hz, 1H), 8.36 – 8.33 (m, 1H), 7.40 – 7.34 (m, 2H), 7.28 – 7.22 (m, 2H), 6.94 – 6.88 (m, 1H), 5.23 (d, J = 5.8 Hz, 1H), 3.65 – 3.55 (m, 1H), 1.96 – 1.84 (m, 2H), 1.75 – 1.64 (m, 2H), 1.58 – 1.50 (m, 1H), 1.43 – 1.31 (m, 2H), 1.26 – 1.14 (m, 3H); ^{13}C NMR (150

MHz, DMSO-d_6) δ 162.03, 160.44, 151.59, 144.13, 134.00, 128.49, 127.31, 123.35, 123.17, 122.91, 122.26, 117.30, 115.67, 112.97, 108.31, 108.13, 103.25, 99.08, 98.92, 54.57, 33.29, 25.50, 24.43.; ^{19}F NMR (565 MHz, DMSO-d_6) δ -114.48 (s, 1F); HRMS (ESI, m/z): calcd for $C_{22}H_{20}FN_5O$ (M+H$^+$) 389.1652, found:389.1657.

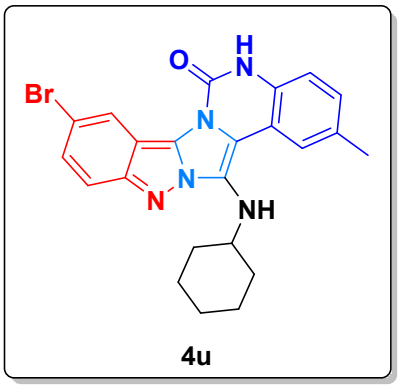
14-(cyclohexylamino)-10-fluoro-2-methylindazolo[3',2':2,3]imidazo[1,5-*c*]quinazolin-6(5*H*)-one (4t)



4t

Yield: 81 % (327.8 mg); Yellow solid; Mp: >300 ^{o}C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.49 (s, 1H), 8.39 – 8.31 (m, 1H), 8.23 (s, 1H), 7.40 – 7.34 (m, 1H), 7.22 – 7.18 (m, 1H), 7.13 (d, J = 8.2 Hz, 1H), 6.94 – 6.89 (m, 1H), 5.25 (d, J = 6.0 Hz, 1H), 3.66 – 3.55 (m, 1H), 2.37 (s, 3H), 1.95 – 1.85 (m, 2H), 1.76 – 1.68 (m, 2H), 1.60 – 1.51 (m, 1H), 1.44 – 1.35 (m, 2H), 1.27 – 1.17 (m, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 143.72, 131.86, 131.42, 128.81, 127.09, 122.97, 122.52, 122.01, 116.67, 115.19, 112.50, 107.79, 107.61, 102.94, 98.48, 54.27, 32.95, 25.07, 23.85, 20.21.; ^{19}F NMR (565 MHz, DMSO-d_6) δ -114.53 (s, 1F); HRMS (ESI, m/z): calcd for $C_{23}H_{22}FN_5O$ (M+H$^+$) 403.1808, found: 403.1804.

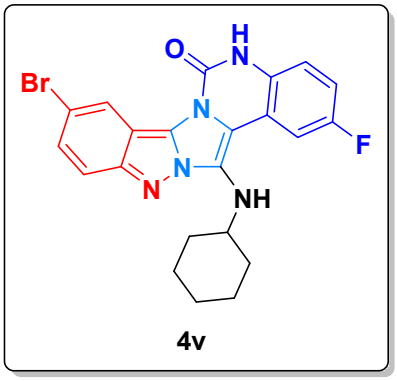
9-bromo-14-(cyclohexylamino)-2-methylindazolo[3',2':2,3]imidazo[1,5-*c*]quinazolin-6(5*H*)-one (4u)



4u

Yield: 85 % (394 mg); Off White solid; Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.32 (s, 1H), 8.50 (s, 1H), 8.24 (s, 1H), 7.60 (d, J = 8.9 Hz, 1H), 7.38 (d, J = 8.9 Hz, 1H), 7.27 – 7.13 (m, 2H), 5.04 (s, 1H), 3.78 – 3.53 (m, 1H), 2.39 (s, 3H), 1.99 – 1.87 (m, 2H), 1.80 – 1.69 (m, 2H), 1.60 – 1.53 (m, 1H), 1.50 – 1.39 (m, 2H), 1.33 – 1.19 (m, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 149.85, 143.79, 132.00, 131.61, 129.19, 128.26, 126.21, 122.78, 121.90, 117.64, 117.32, 115.35, 112.45, 109.28, 106.67, 54.36, 33.07, 25.19, 24.00, 20.39.; HRMS (ESI, m/z): calcd for $C_{23}H_{22}BrN_5O$ ($M+H^+$) 463.1008, found: 463.1004.

9-bromo-14-(cyclohexylamino)-2-fluoroindazolo[3',2':2,3]imidazo[1,5-*c*]quinazolin-6(5*H*)-one (4v)

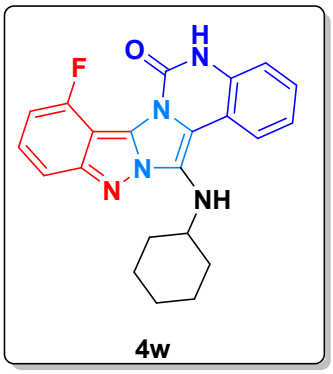


4v

Yield: 82 % (383 mg); Yellow solid; Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.40 (s, 1H), 8.50 (s, 1H), 8.17 (d, J = 8.5 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.33 – 7.18 (m, 2H), 5.20 (s, 1H), 3.80 – 3.67 (m, 1H), 2.01 – 1.89 (m, 2H), 1.80 – 1.69 (m, 2H), 1.64 – 1.51 (m, 1H), 1.50 – 1.37 (m, 2H), 1.33 – 1.22 (m, 3H).; ^{13}C NMR (150 MHz, DMSO-d_6) δ 154.81, 153.93, 153.11, 143.16, 134.06, 128.78, 125.80, 124.30, 123.11, 122.91, 121.79, 118.59, 115.29, 112.65, 111.91, 103.00, 102.87, 96.84, 96.73, 54.68, 33.28, 25.51, 24.46.; ^{19}F

NMR (565 MHz, DMSO-d_6) δ -118.74 (s, 1F); HRMS (ESI, m/z): calcd for $C_{22}H_{19}BrFN_5O$ ($M+H^+$) 467.0757, found: 467.0752.

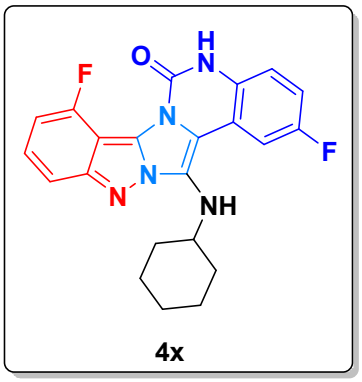
14-(cyclohexylamino)-8-fluoroindazolo[3',2':2,3]imidazo[1,5-*c*]quinazolin-6(5*H*)-one (4w)



4w

Yield: 84 % (328 mg); Off White solid; Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.20 (s, 1H), 8.47 (d, J = 7.8 Hz, 1H), 7.47 (d, J = 8.6 Hz, 1H), 7.43 – 7.37 (m, 1H), 7.33 – 7.24 (m, 3H), 6.79 – 6.73 (m, 1H), 4.98 (d, J = 5.2 Hz, 1H), 3.69 – 3.59 (m, 1H), 1.99 – 1.88 (m, 2H), 1.80 – 1.68 (m, 2H), 1.61 – 1.51 (m, 1H), 1.50 – 1.37 (m, 2H), 1.30 – 1.20 (m, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 154.65, 153.75, 152.95, 142.85, 133.83, 128.38, 125.38, 124.15, 122.83, 122.56, 121.64, 118.16, 115.02, 112.41, 111.59, 102.60, 102.47, 96.58, 54.41, 33.03, 25.19, 24.10.; ^{19}F NMR (565 MHz, DMSO-d_6) δ -107.23 (s, 1F); HRMS (ESI, m/z): calcd for $C_{22}H_{20}FN_5O$ ($M+H^+$) 389.1652, found: 389.1648.

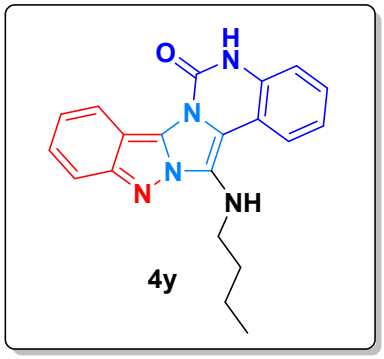
14-(cyclohexylamino)-2,8-difluoroindazolo[3',2':2,3]imidazo[1,5-*c*]quinazolin-6(5*H*)-one (4x)



4x

Yield: 87 % (354.8 mg); Off White solid; Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.23 (s, 1H), 8.23 – 8.18 (m, 1H), 7.47 (d, J = 8.6 Hz, 1H), 7.32 – 7.21 (m, 3H), 6.79 – 6.73 (m, 1H), 5.15 (d, J = 4.5 Hz, 1H), 3.74 – 3.65 (m, 1H), 1.99 – 1.89 (m, 2H), 1.80 – 1.70 (m, 2H), 1.62 – 1.52 (m, 1H), 1.49 – 1.39 (m, 2H), 1.32 – 1.21 (m, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 158.14, 156.56, 154.60, 153.85, 152.89, 142.49, 130.29, 125.44, 122.24, 116.58, 115.41, 115.25, 113.47, 111.51, 108.52, 108.35, 102.44, 96.38, 54.13, 32.95, 25.02, 23.91.; ^{19}F NMR (565 MHz, DMSO-d_6) δ -107.06 (s, 1F), -119.14 (s, 1F); HRMS (ESI, m/z): calcd for $C_{22}H_{19}F_2N_5O$ ($M+H^+$) 407.1558, found: 407.1562.

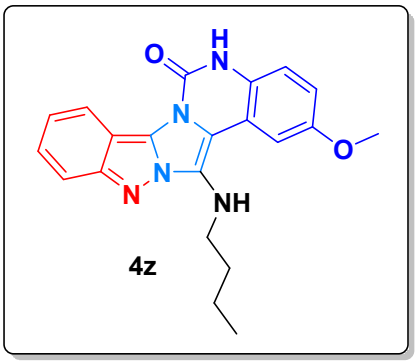
14-(butylamino)indazolo[3',2':2,3]imidazo[1,5-*c*]quinazolin-6(5*H*)-one (4y)



4y

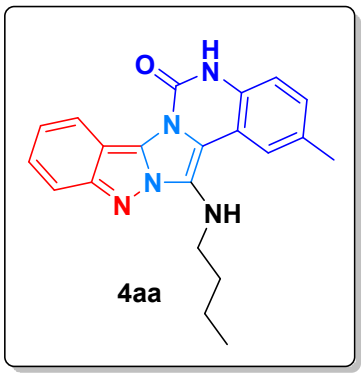
Yield: 90 % (311.0 mg); White solid; Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.15 (s, 1H), 8.40 – 8.35 (m, 1H), 8.34 – 8.29 (m, 1H), 7.64 – 7.59 (m, 1H), 7.38 – 7.34 (m, 1H), 7.32 (t, J = 7.4 Hz, 1H), 7.29 – 7.23 (m, 2H), 7.06 – 6.98 (m, 1H), 5.14 (s, 1H), 3.56 – 3.48 (m, 2H), 1.69 – 1.60 (m, 2H), 1.49 – 1.39 (m, 2H), 0.90 (t, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 151.63, 143.69, 133.49, 127.53, 127.00, 125.28, 123.34, 122.57, 122.14, 120.91, 117.32, 115.12, 114.88, 114.71, 112.79, 112.64, 105.28, 45.38, 31.95, 19.05, 13.04.; HRMS (ESI, m/z): calcd for $C_{20}H_{19}N_5O$ ($M+H^+$) 345.1590, found: 345.1594.

14-(butylamino)-2-methoxyindazolo[3',2':2,3]imidazo[1,5-*c*]quinazolin-6(5*H*)-one (4z)



Yield: 86 % (323.2 mg); White solid; Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.34 (s, 1H), 8.35 (d, J = 8.2 Hz, 1H), 7.87 (s, 1H), 7.61 (d, J = 8.5 Hz, 1H), 7.36 – 7.28 (m, 1H), 7.18 (d, J = 8.7 Hz, 1H), 7.09 – 6.97 (m, 2H), 5.53 (s, 1H), 3.84 (s, 3H), 3.52 – 3.43 (m, 2H), 1.66 – 1.51 (m, 2H), 1.48 – 1.34 (m, 2H), 0.87 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 155.03, 151.70, 143.60, 127.44, 127.12, 125.43, 123.29, 121.08, 117.40, 116.38, 115.15, 115.02, 114.94, 113.52, 106.53, 105.33, 55.29, 45.45, 32.11, 19.19, 13.22.; HRMS (ESI, m/z): calcd for $C_{21}H_{21}N_5O_2$ ($M+H^+$) 375.1695, found: 375.1691.

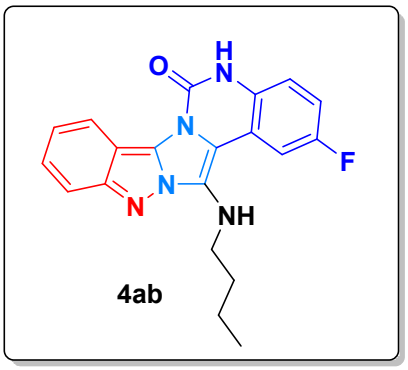
14-(butylamino)-2-methylindazolo[3',2':2,3]imidazo[1,5-*c*]quinazolin-6(5*H*)-one (4aa)



Yield: 88 % (316.3 mg); White solid; Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.28 (s, 1H), 8.35 (d, J = 8.2 Hz, 1H), 8.15 (s, 1H), 7.61 (d, J = 8.6 Hz, 1H), 7.36 – 7.27 (m, 1H), 7.24 – 7.11 (m, 2H), 7.07 – 6.96 (m, 1H), 5.35 (s, 1H), 3.54 – 3.44 (m, 2H), 2.38 (s, 3H), 1.67 – 1.55 (m, 2H), 1.51 – 1.38 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 151.60, 143.66, 131.79, 131.24, 130.26, 128.38, 126.99, 125.22, 123.18, 122.11, 120.91, 117.25,

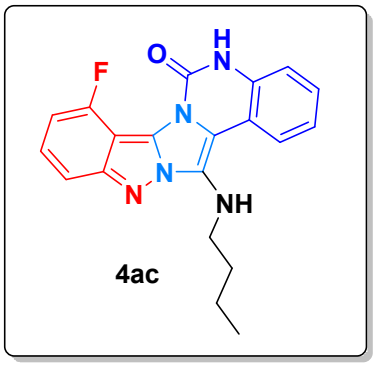
114.99, 114.83, 112.60, 105.30, 45.37, 31.90, 19.97, 19.03, 13.02.; HRMS (ESI, m/z): calcd for $C_{21}H_{21}N_5O$ ($M+H^+$) 359.1746, found: 359.1743.

14-(butylamino)-2-fluoroindazolo[3',2':2,3]imidazo[1,5-*c*]quinazolin-6(5*H*)-one (4ab)



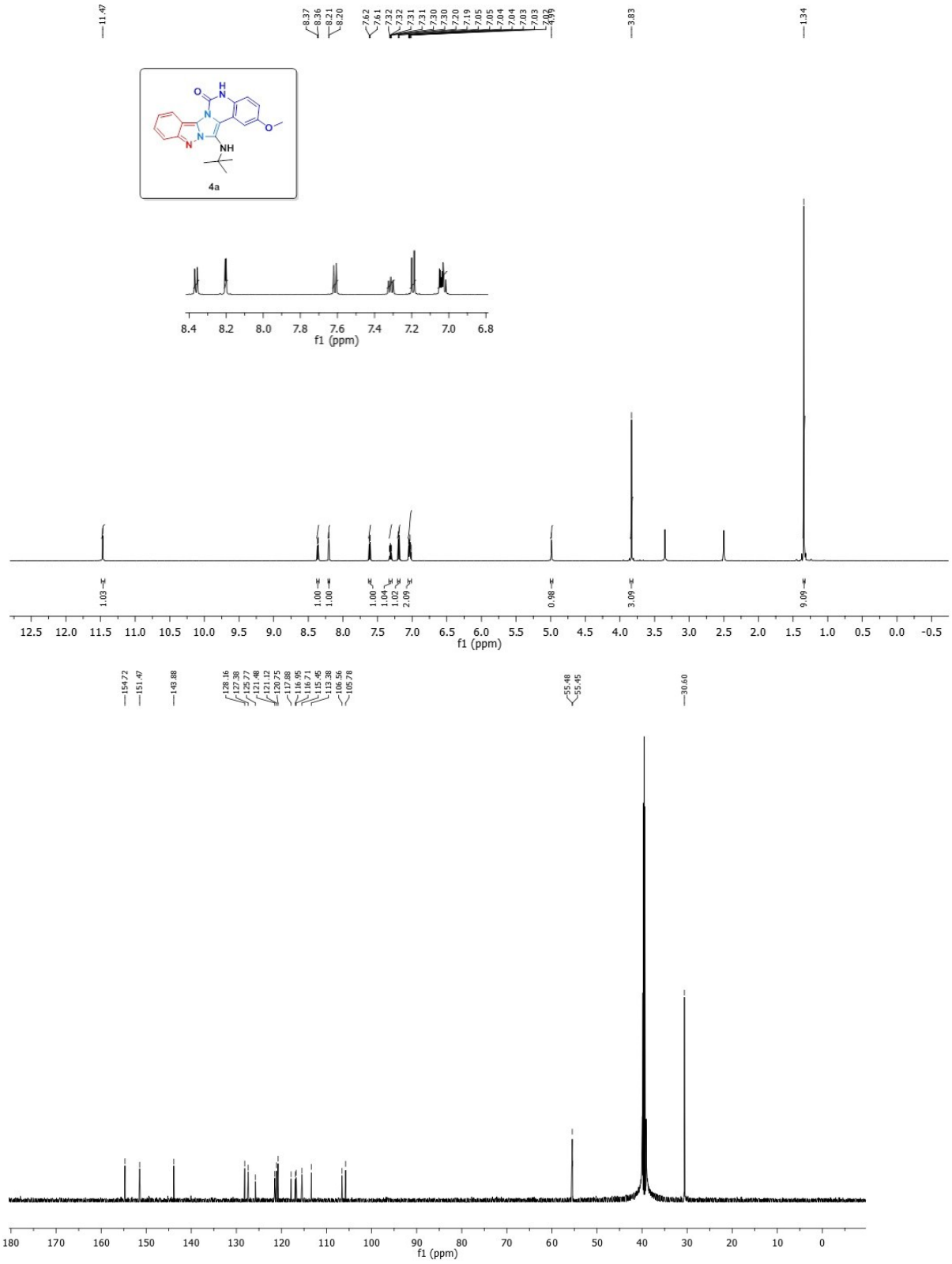
Yield: 84 % (305.6 mg); White solid; Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.49 (s, 1H), 8.34 (d, J = 8.3 Hz, 1H), 8.08 (d, J = 9.6 Hz, 1H), 7.62 (d, J = 8.6 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.27 – 7.18 (m, 2H), 7.03 (t, J = 7.4 Hz, 1H), 5.69 (s, 1H), 3.60 – 3.48 (m, 2H), 1.61 – 1.51 (m, 2H), 1.44 – 1.35 (m, 2H), 0.87 (t, J = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 158.43, 151.83, 143.46, 131.78, 129.96, 127.28, 125.50, 124.04, 120.97, 117.40, 116.71, 116.65, 114.91, 114.47, 114.32, 108.00, 107.82, 105.09, 45.04, 32.00, 19.00, 13.00.; HRMS (ESI, m/z): calcd for $C_{20}H_{18}FN_5O$ ($M+H^+$) 363.1495, found: 363.1492.

14-(butylamino)-8-fluoroindazolo[3',2':2,3]imidazo[1,5-*c*]quinazolin-6(5*H*)-one (4ac)

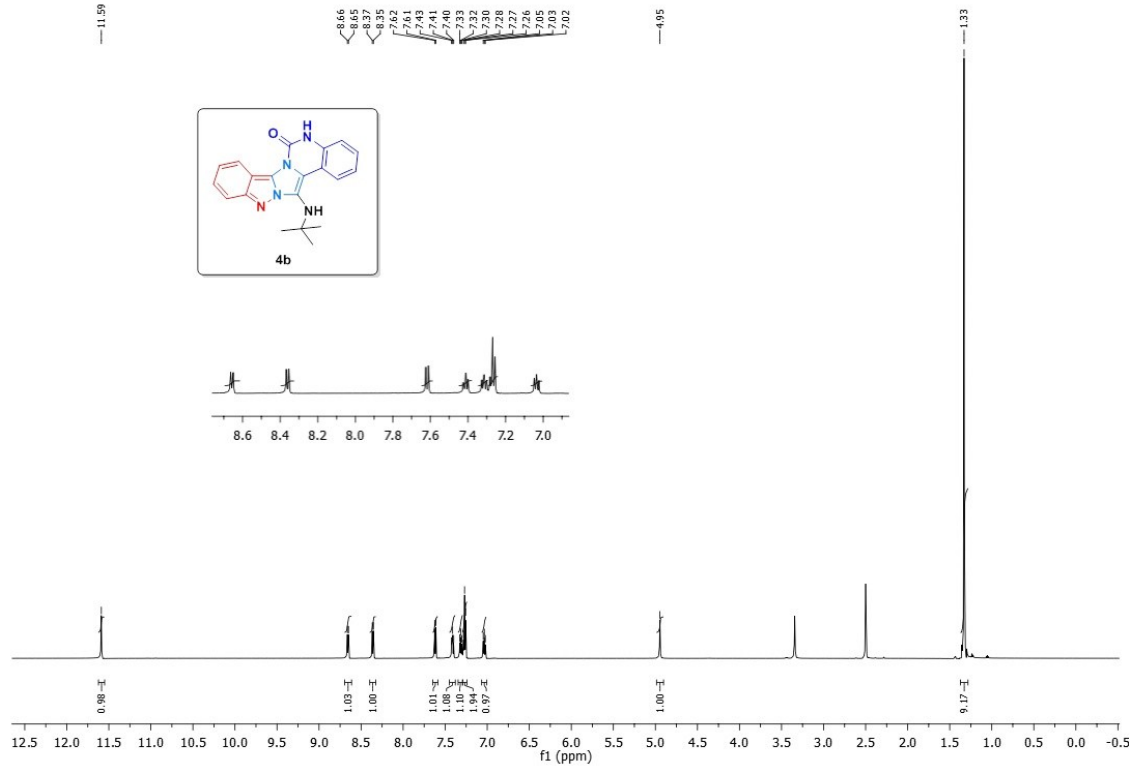


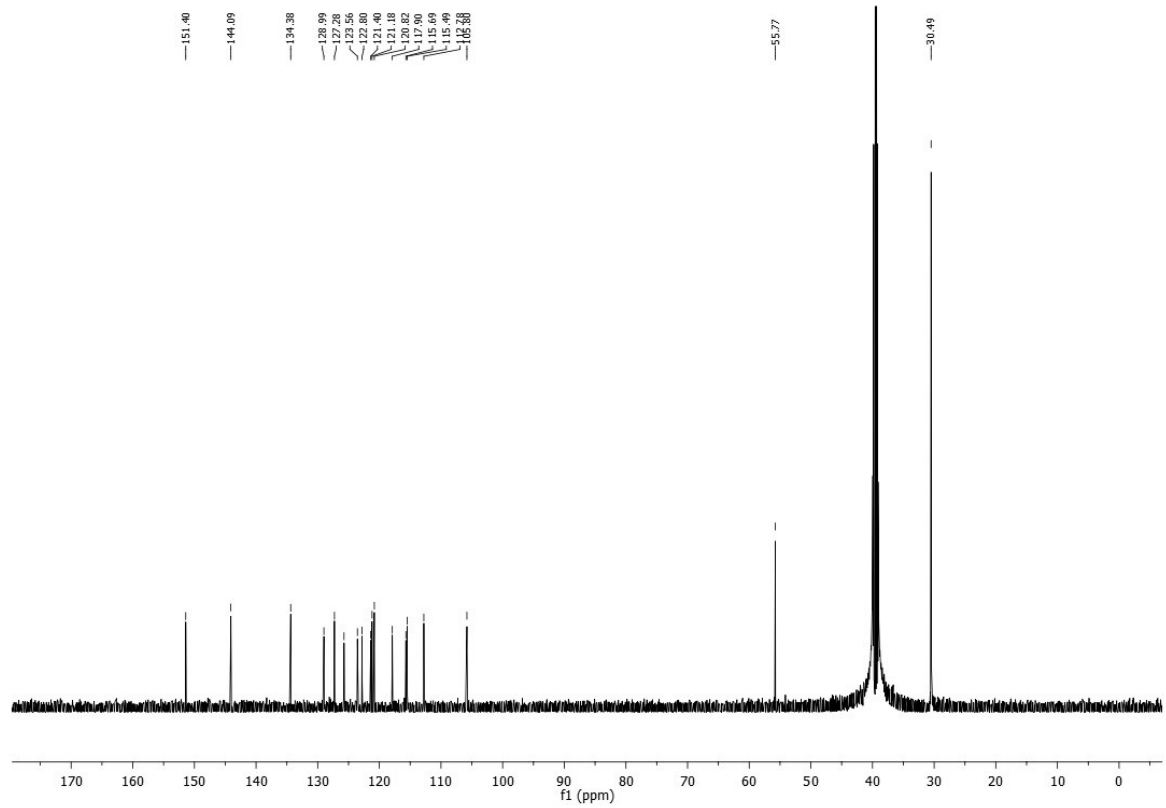
Yield: 91 % (330.2 mg); White solid; Mp: >300 ^{o}C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.39 (s, 1H), 8.36 – 8.33 (m, 1H), 7.46 (d, J = 8.5 Hz, 1H), 7.38 – 7.34 (m, 1H), 7.30 – 7.22 (m, 3H), 6.79 – 6.74 (m, 1H), 5.43 (t, J = 6.0 Hz, 1H), 3.44 – 3.38 (m, 2H), 1.59 – 1.53 (m, 2H), 1.42 – 1.34 (m, 2H), 0.85 (t, J = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 154.81, 153.97, 153.94, 153.11, 143.14, 133.86, 128.44, 125.79, 125.73, 124.30, 124.28, 123.19, 122.90, 122.70, 116.39, 115.22, 112.73, 111.81, 111.78, 102.93, 102.80, 96.74, 96.63, 45.78, 32.35, 19.68, 13.83.; HRMS (ESI, m/z): calcd for $C_{20}H_{18}FN_5O$ ($M+H^+$) 363.1495, found: 363.1491.

^{1}H NMR and ^{13}C NMR of compound (4a)

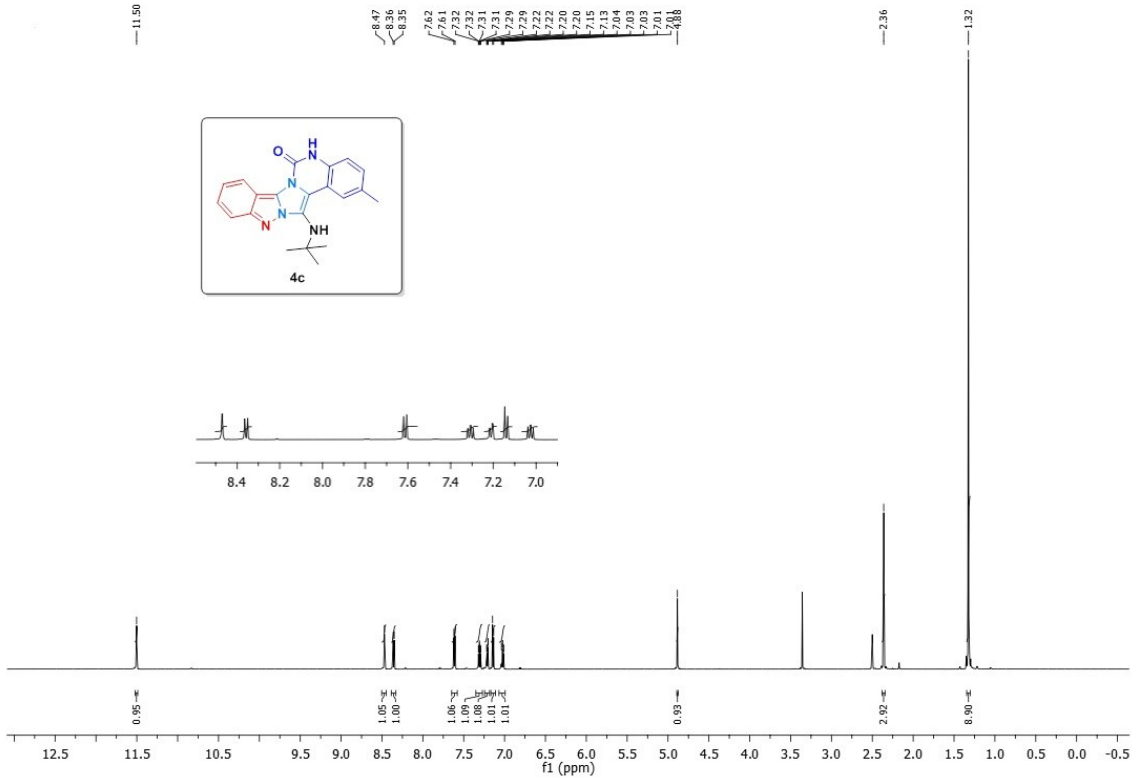


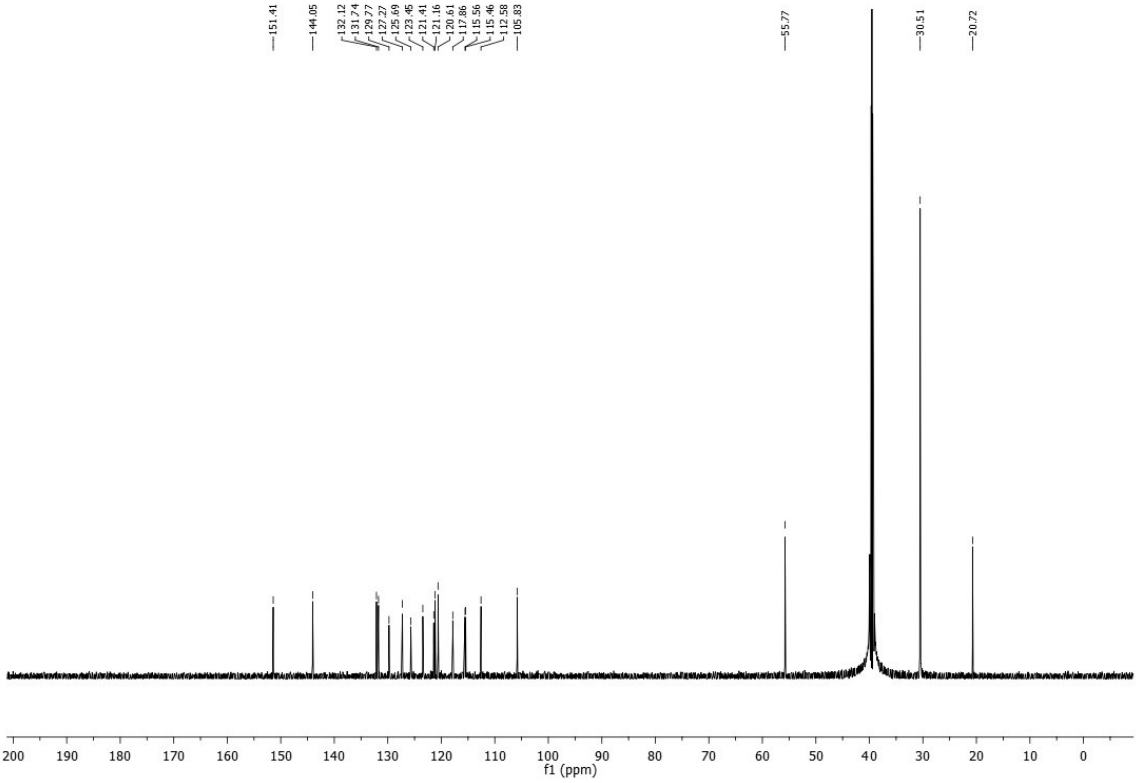
^{1}H NMR and ^{13}C NMR of compound (**4b**)



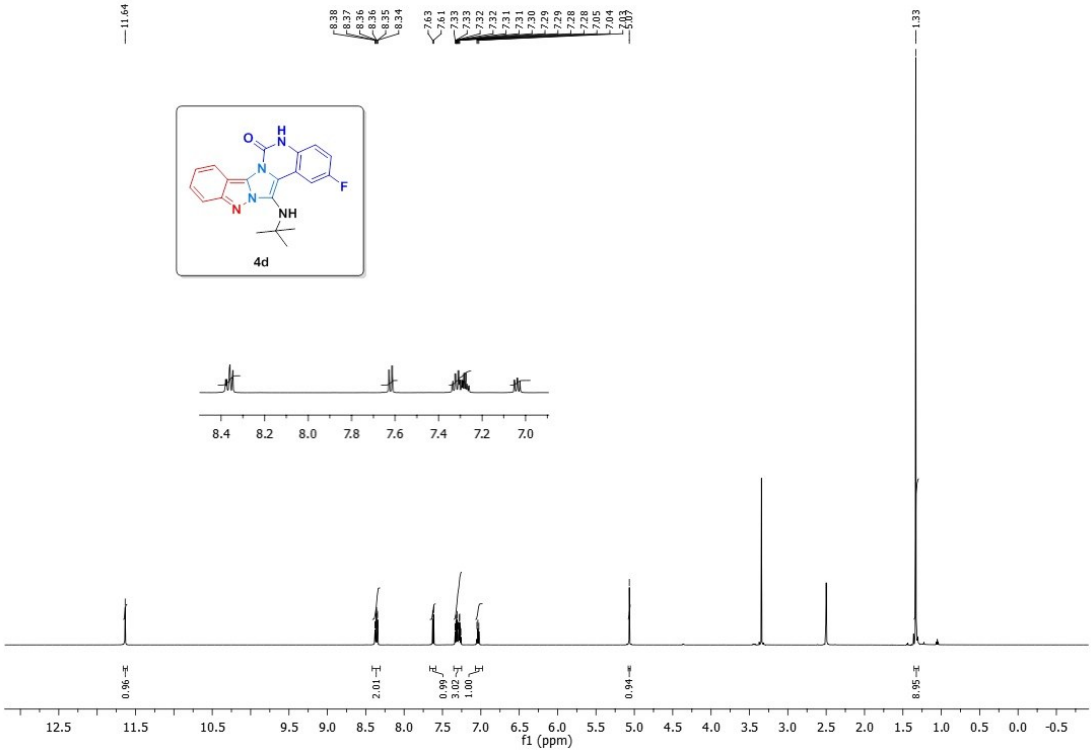


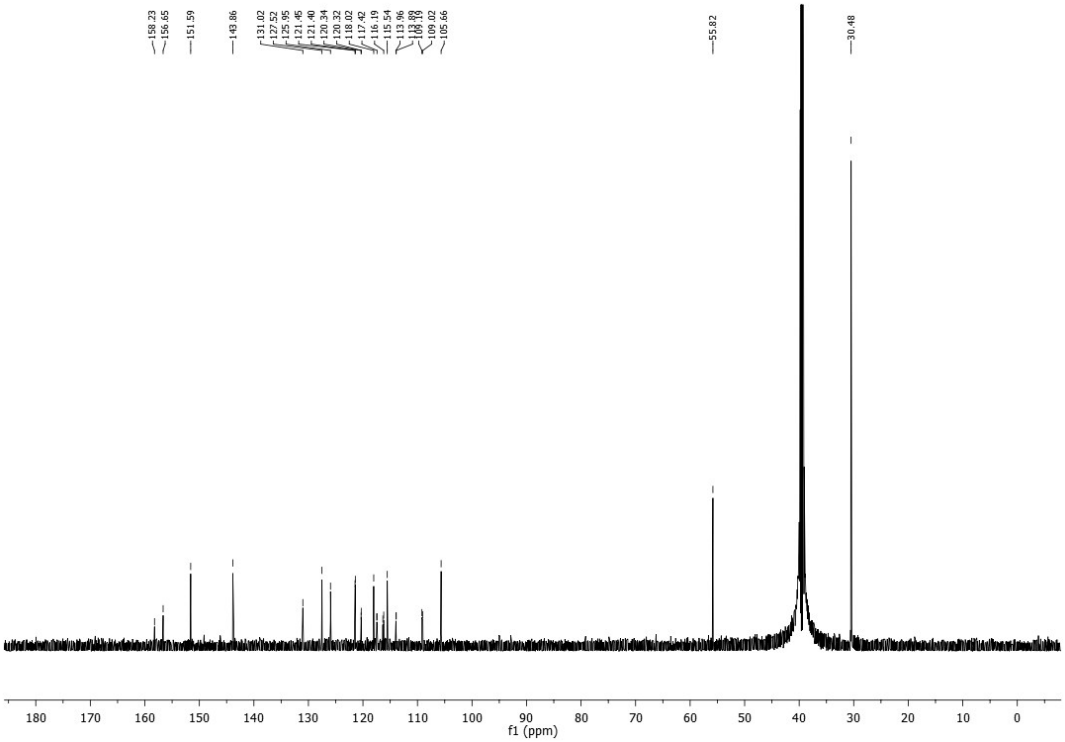
^{1}H NMR and ^{13}C NMR of compound (**4c**)



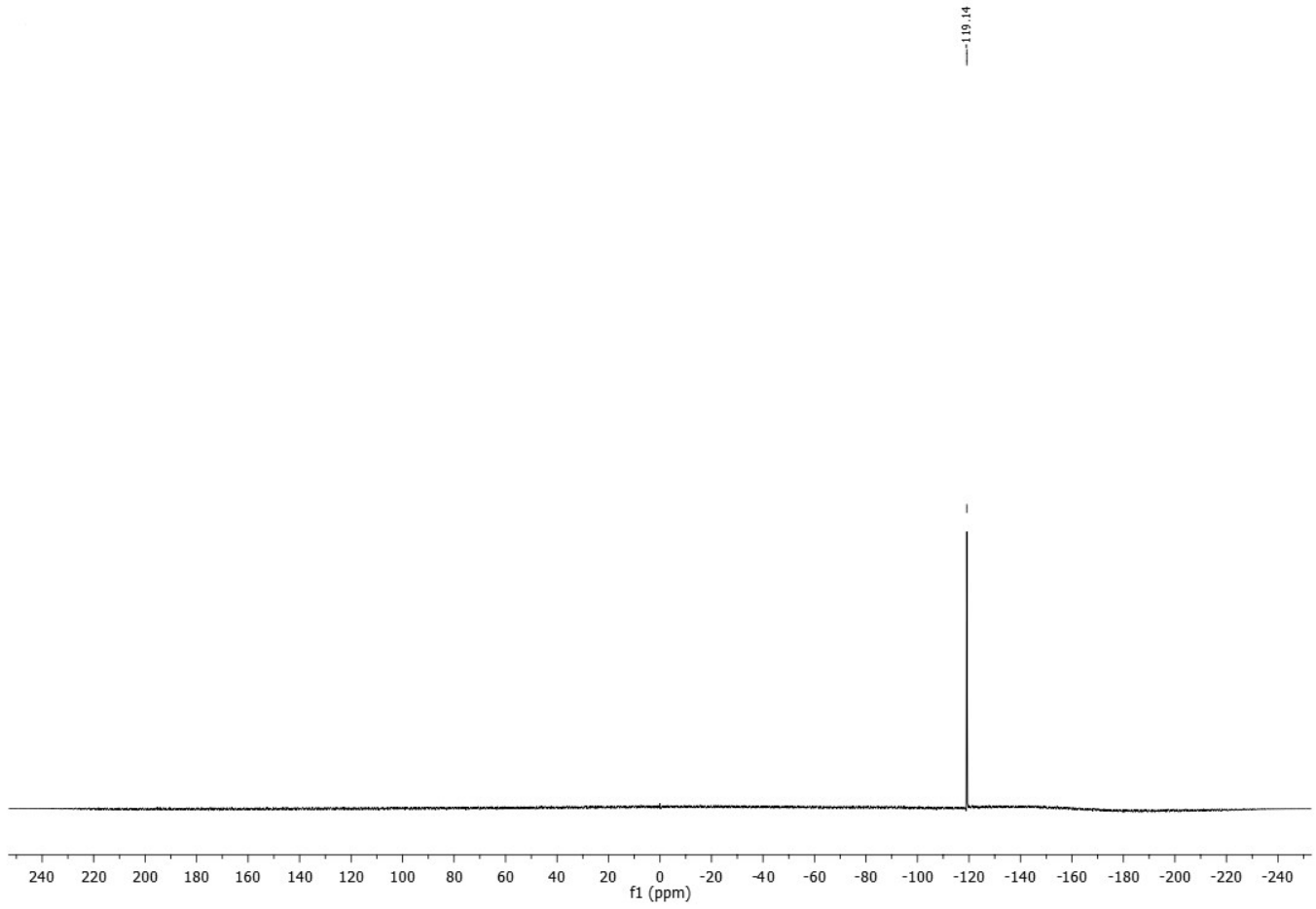


^{1}H NMR and ^{13}C NMR of compound (**4d**)

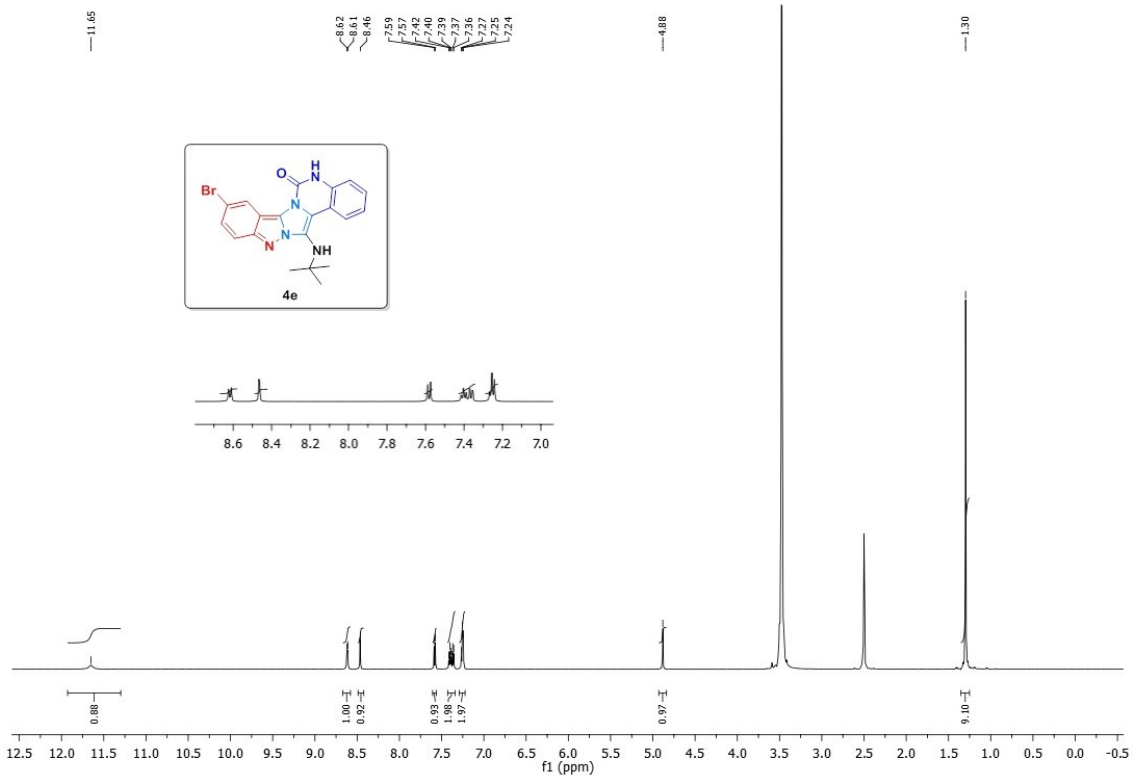


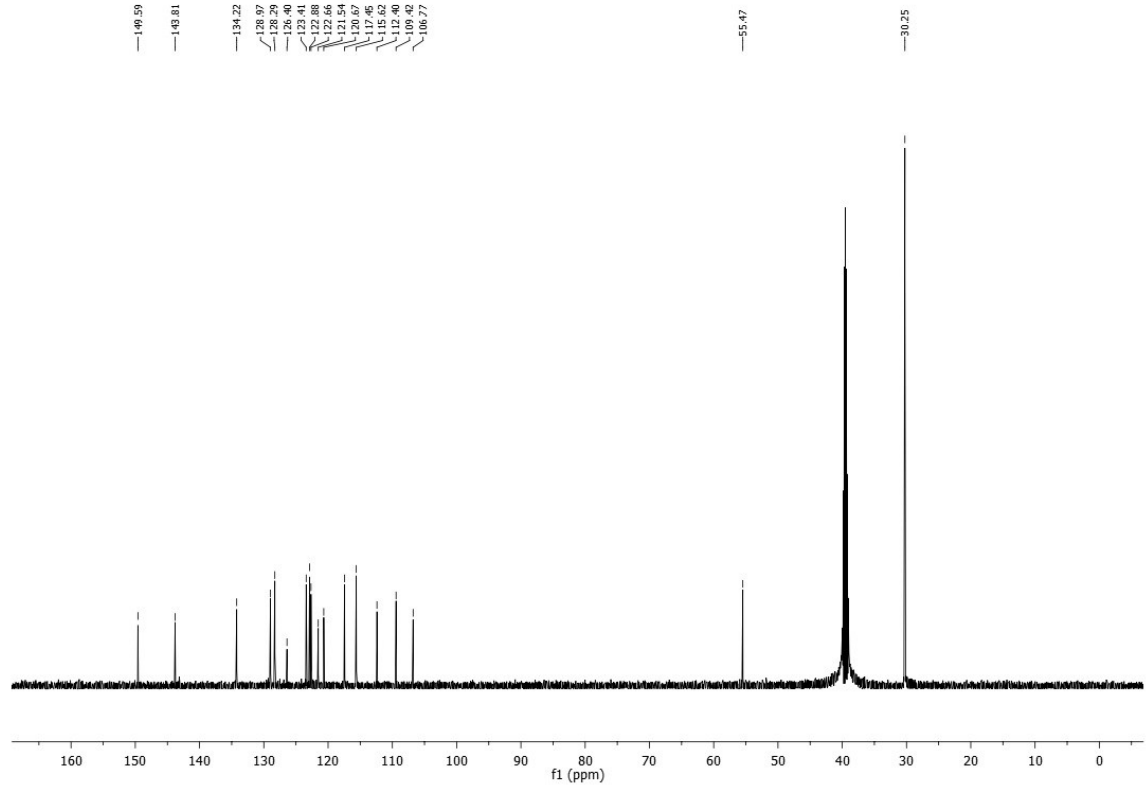


^{19}F NMR of compound (**4d**)

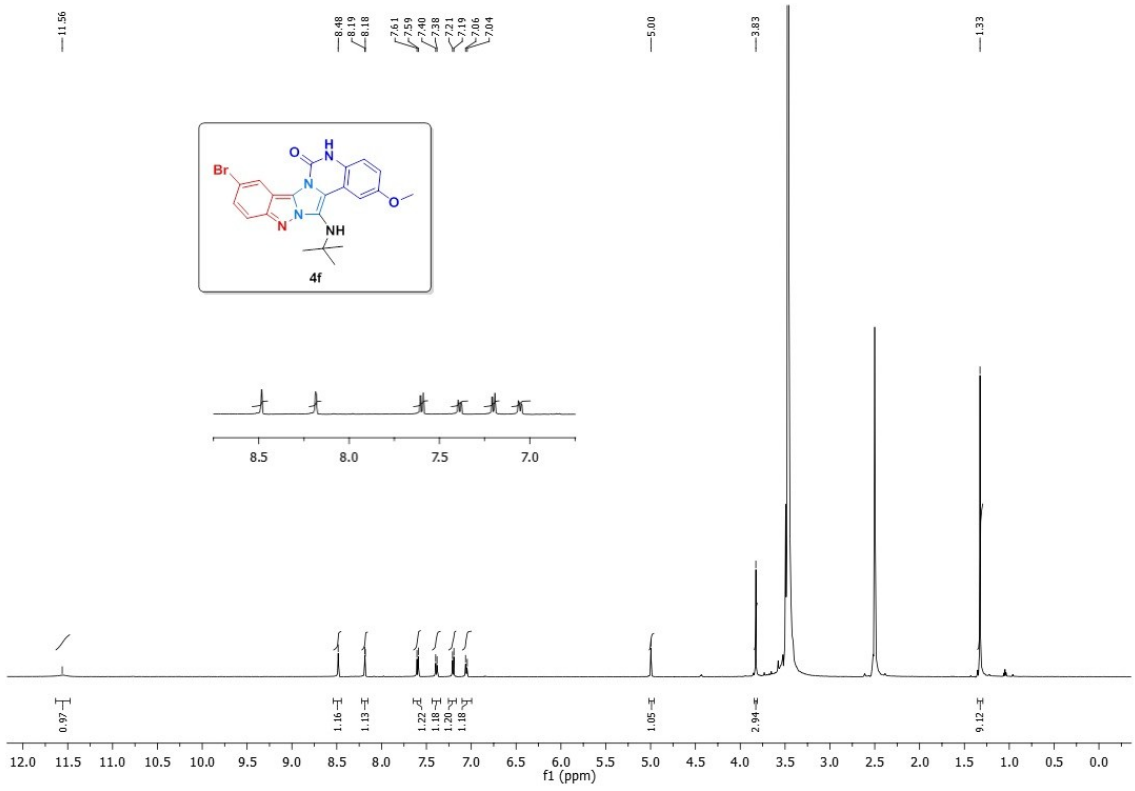


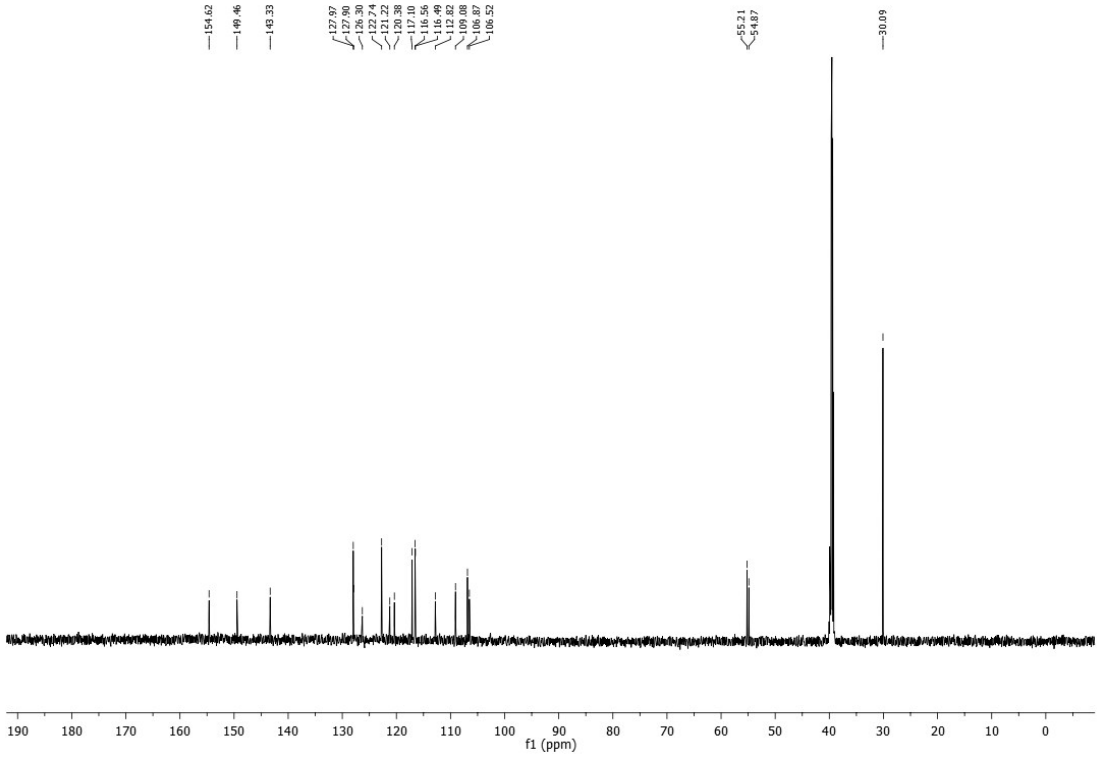
^{1}H NMR and ^{13}C NMR of compound (**4e**)



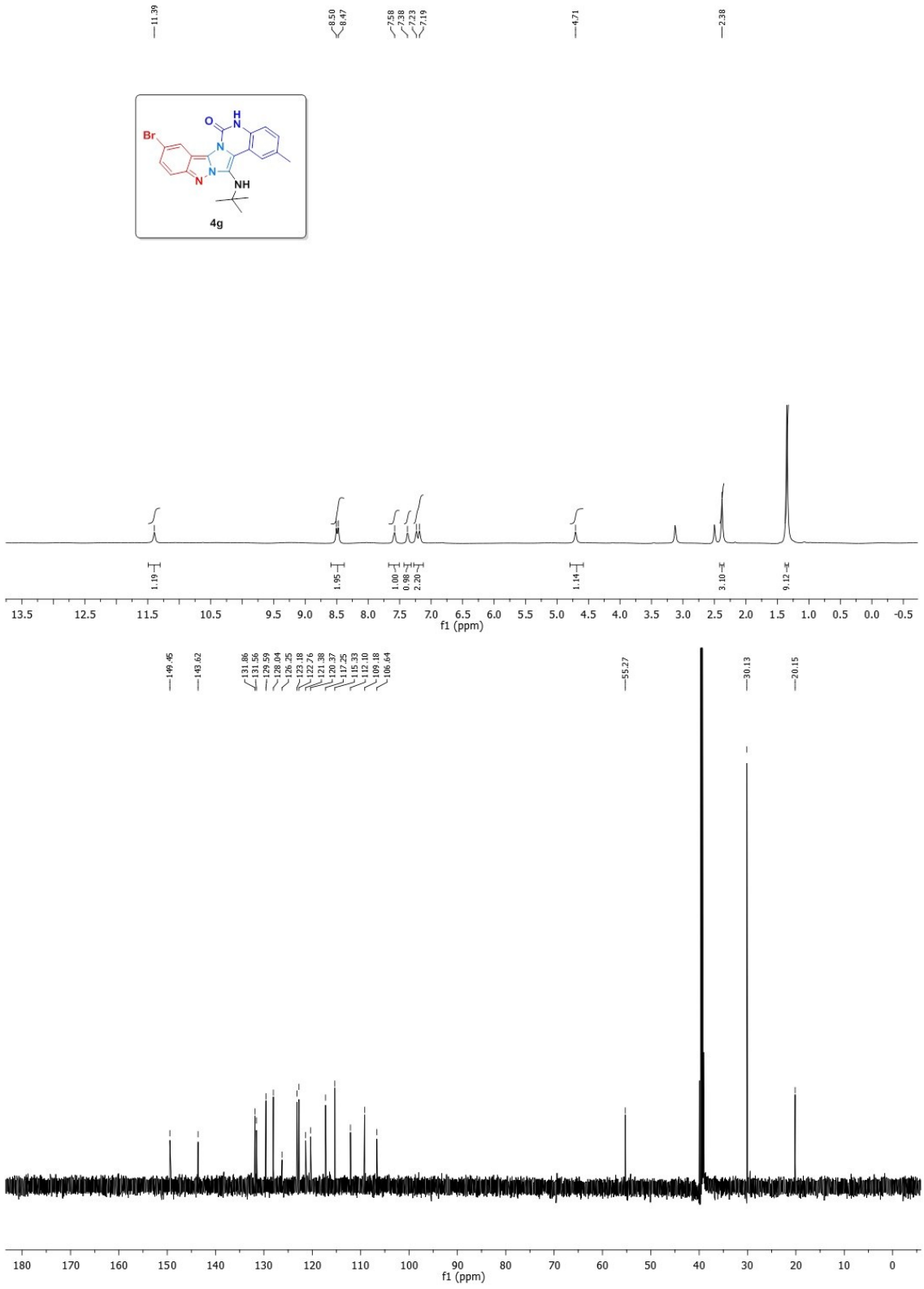


^{1}H NMR and ^{13}C NMR of compound (**4f**)

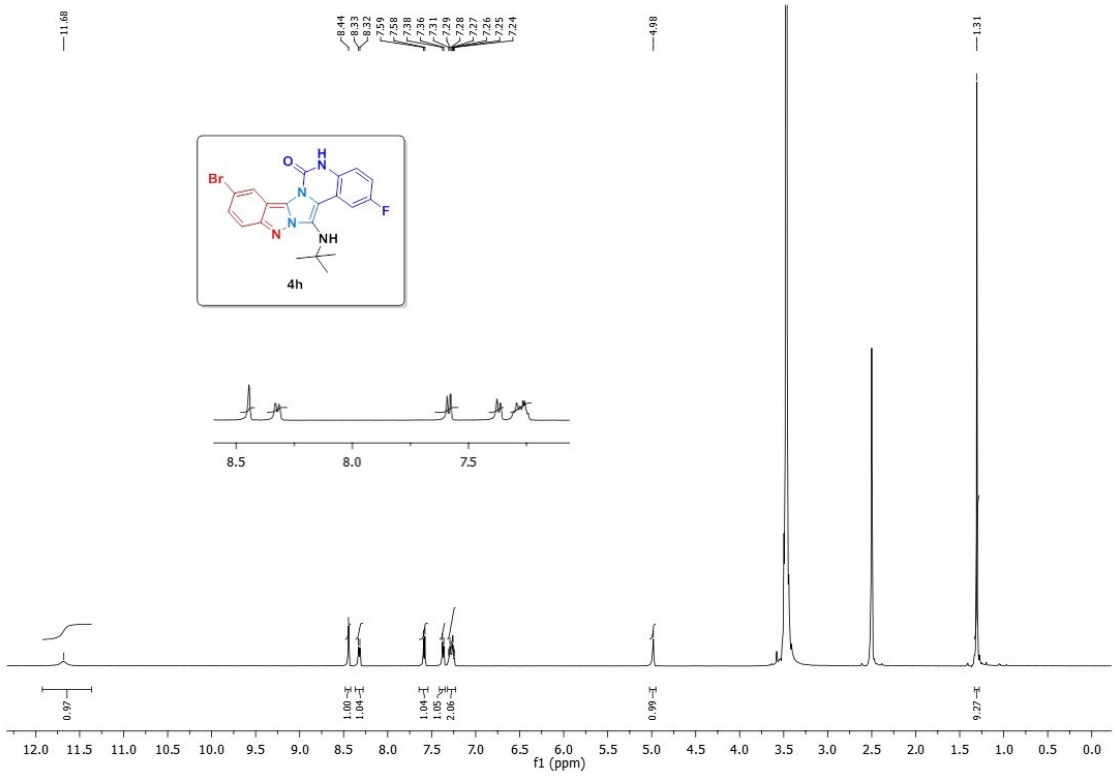


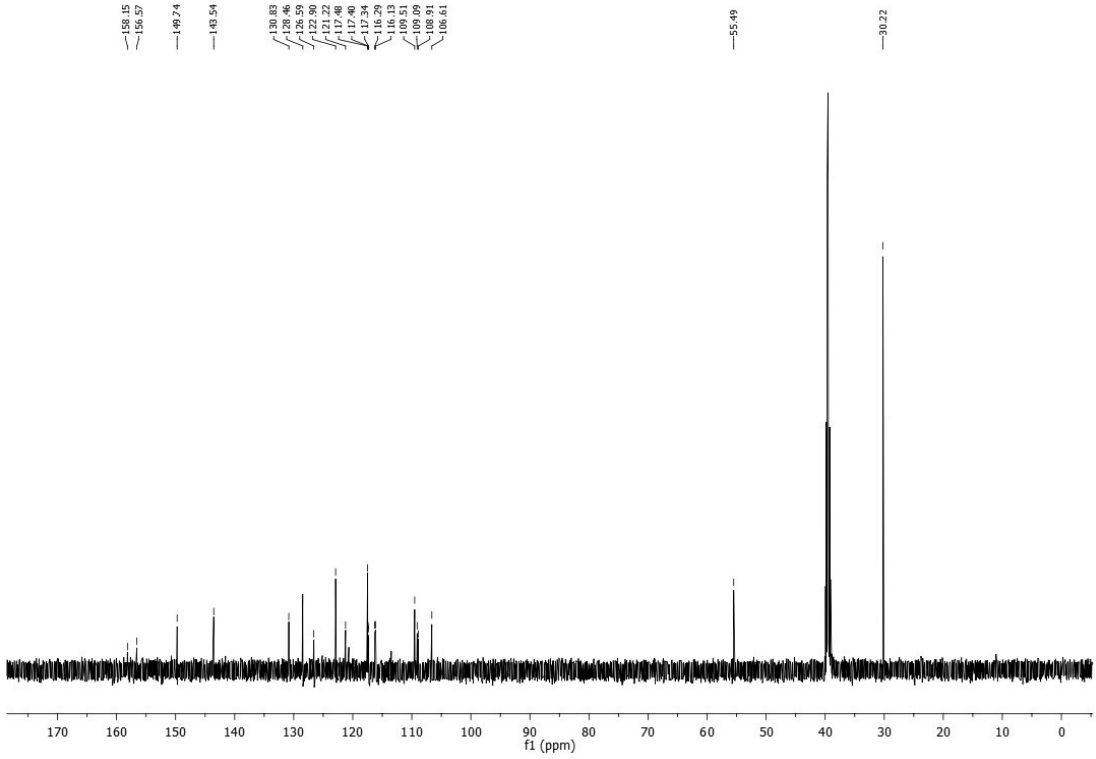


^{1}H NMR and ^{13}C NMR of compound (**4g**)

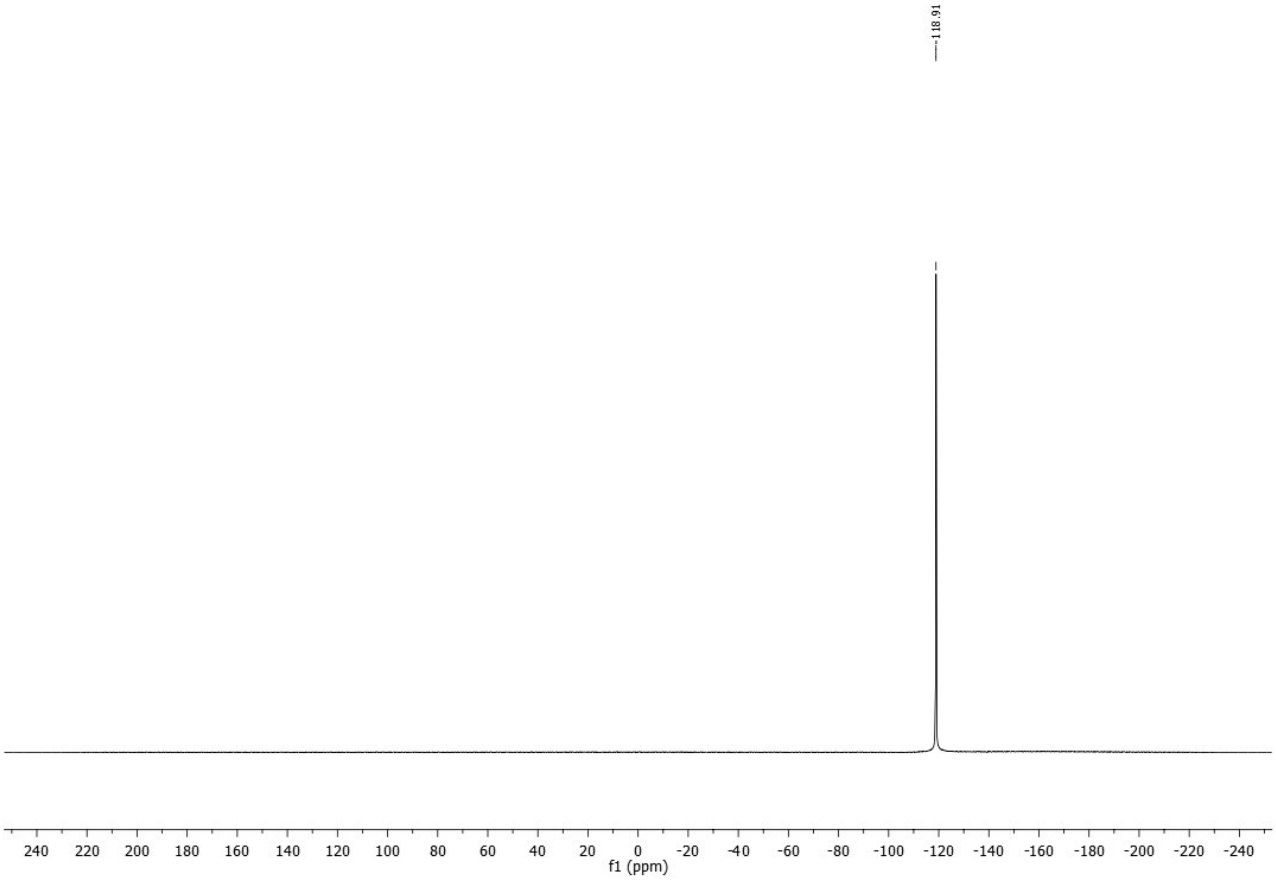


^{1}H NMR and ^{13}C NMR of compound (**4h**)

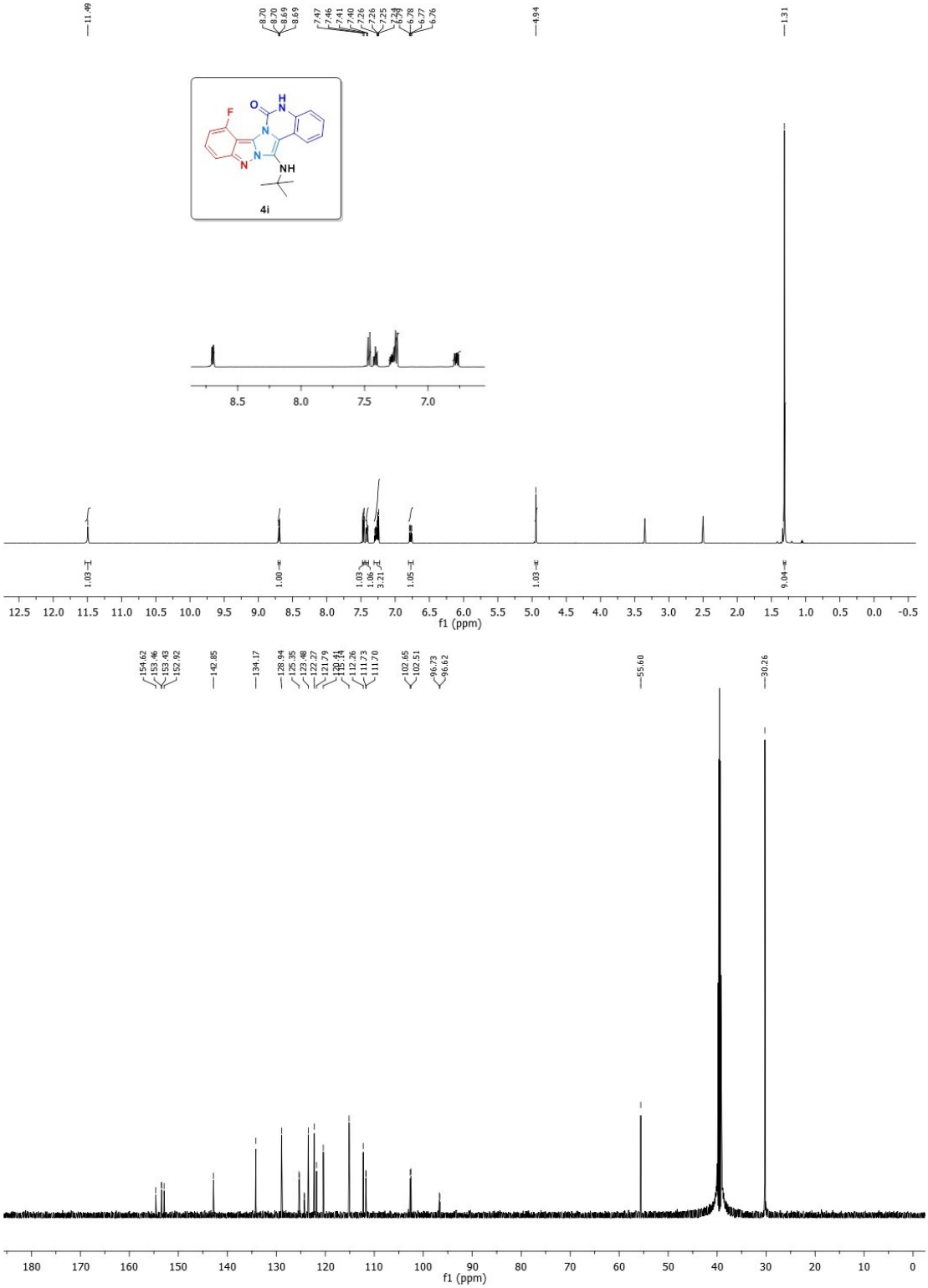




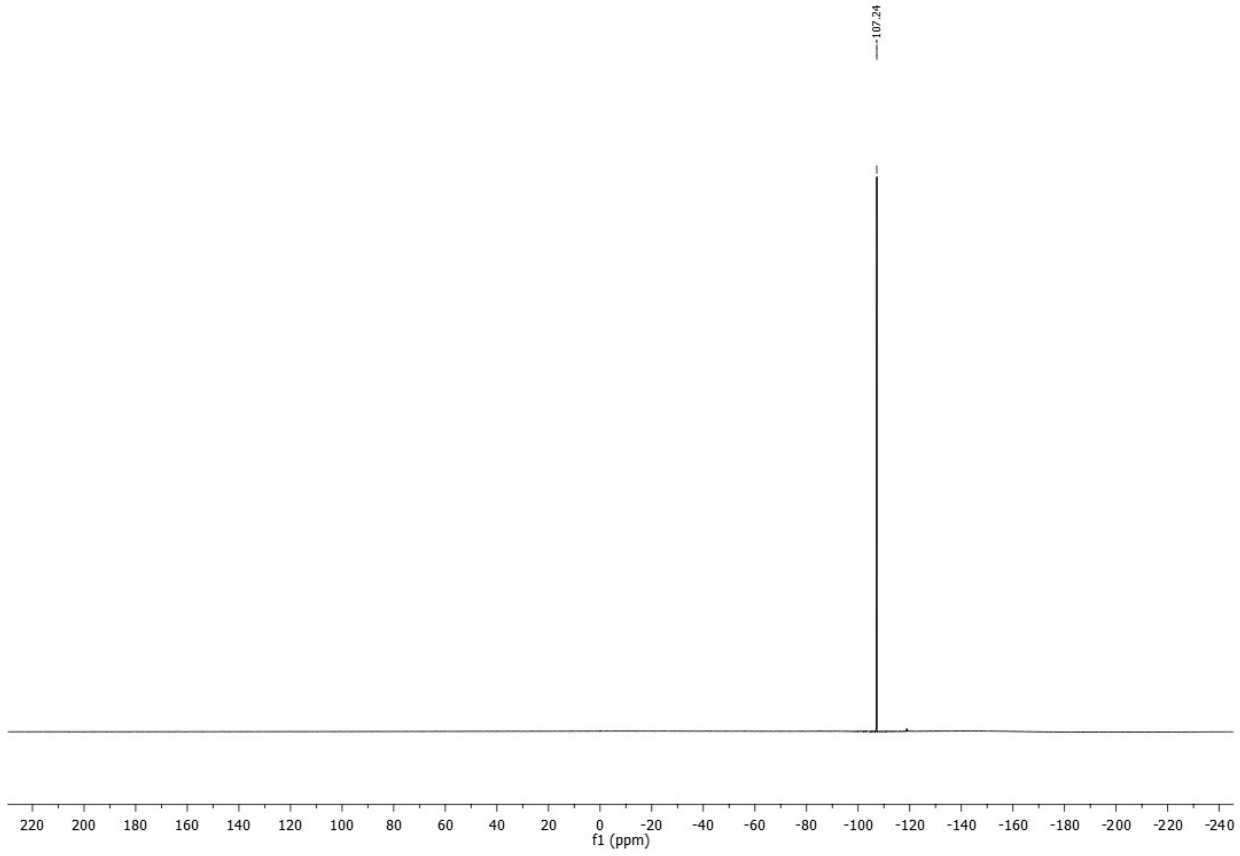
^{19}F NMR of compound (**4h**)



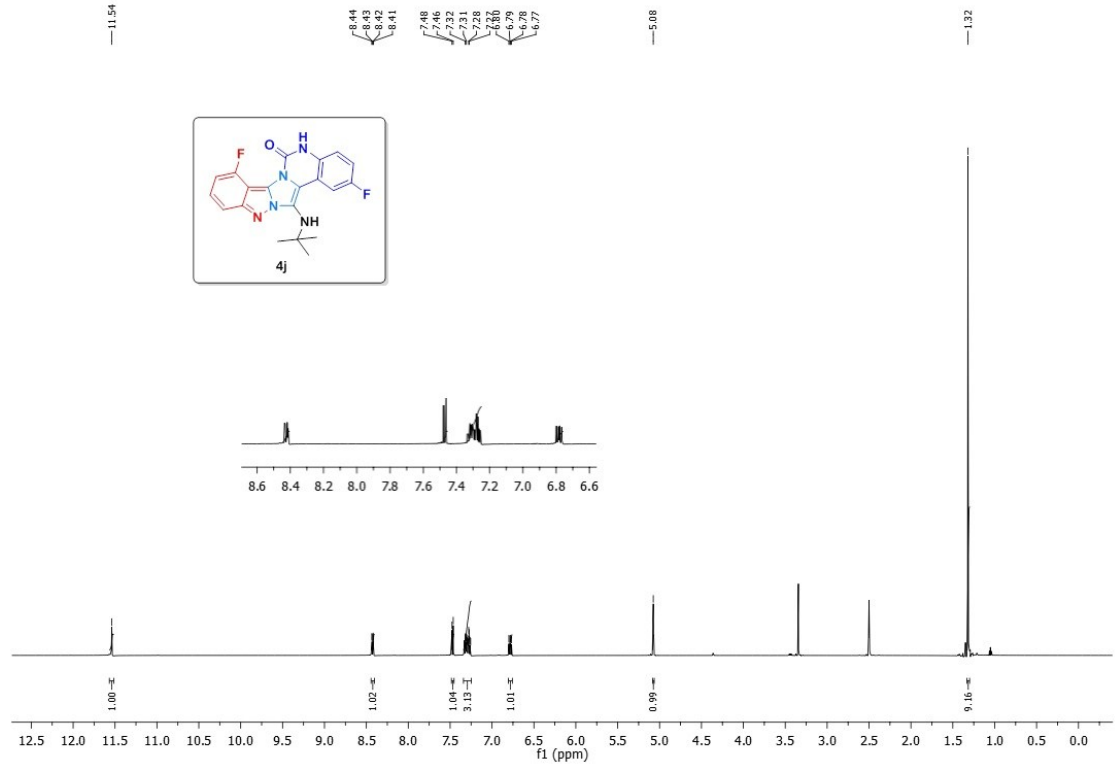
^{1}H NMR and ^{13}C NMR of compound (**4i**)

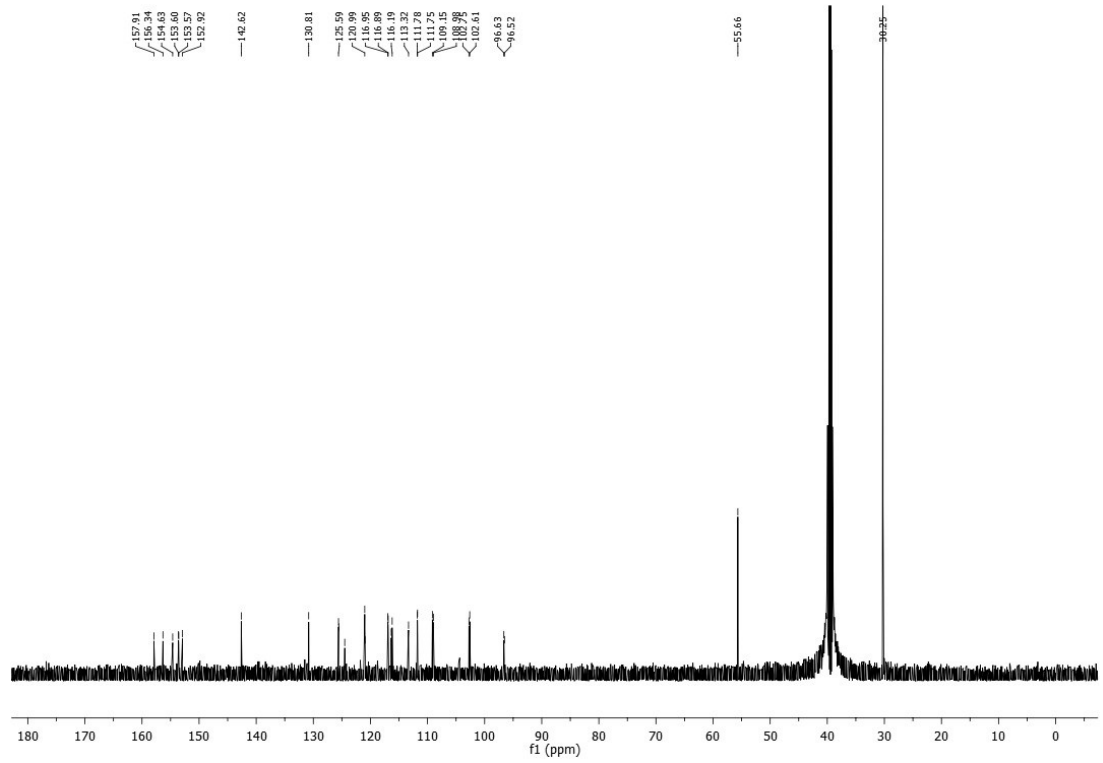


^{19}F NMR of compound (**4i**)

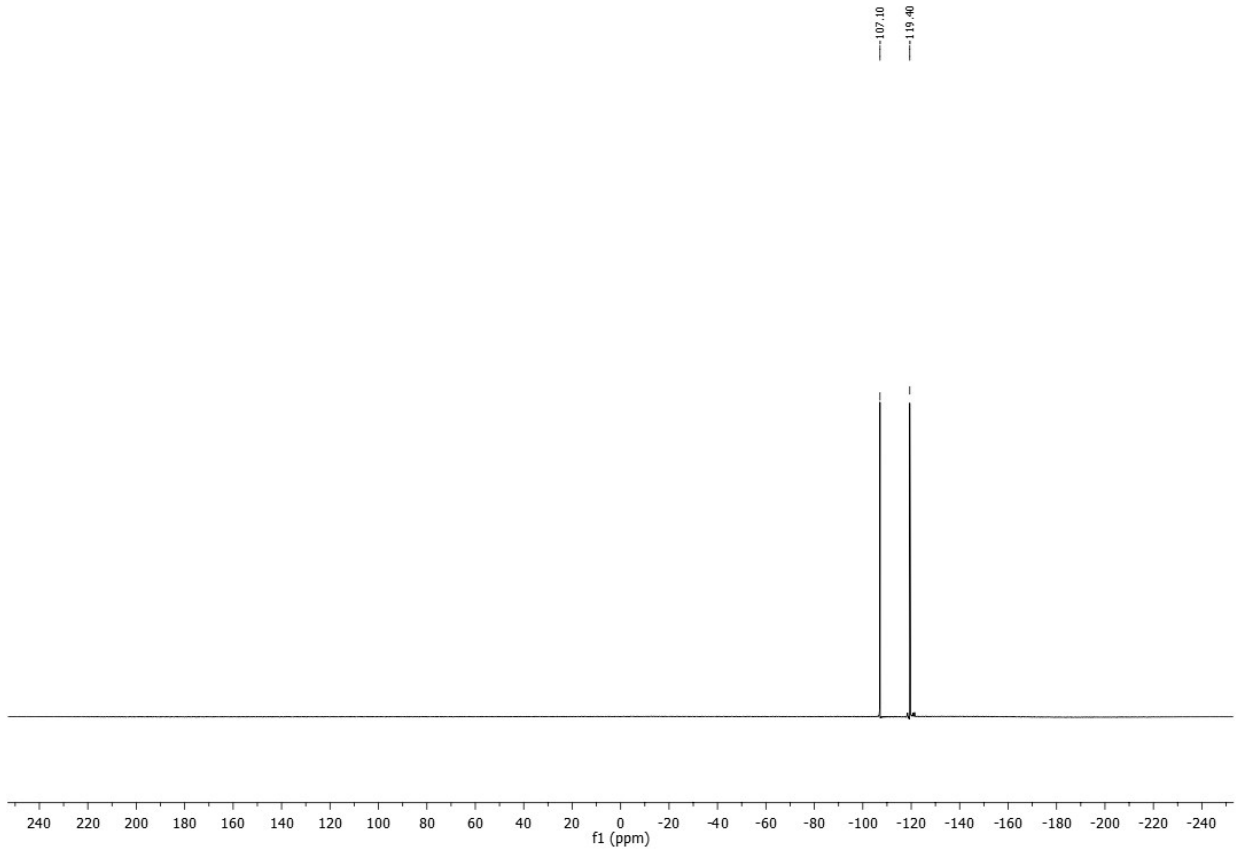


^{1}H NMR and ^{13}C NMR of compound (**4j**)

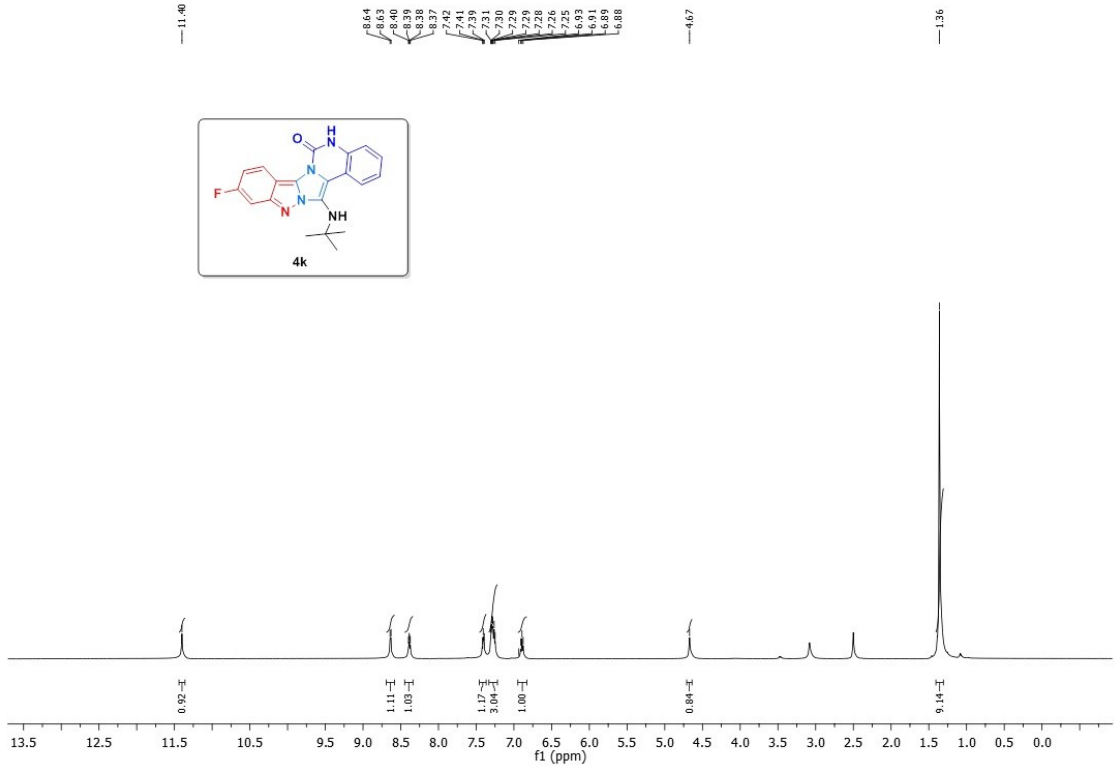


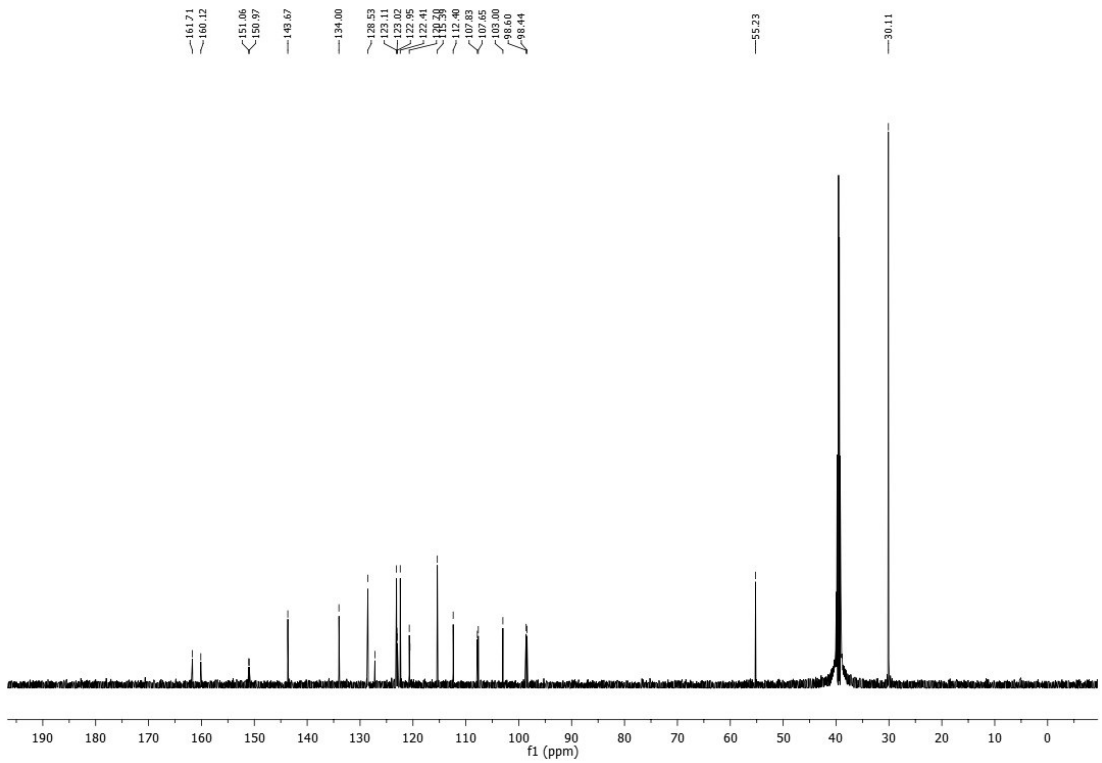


^{19}F NMR of compound (**4j**)

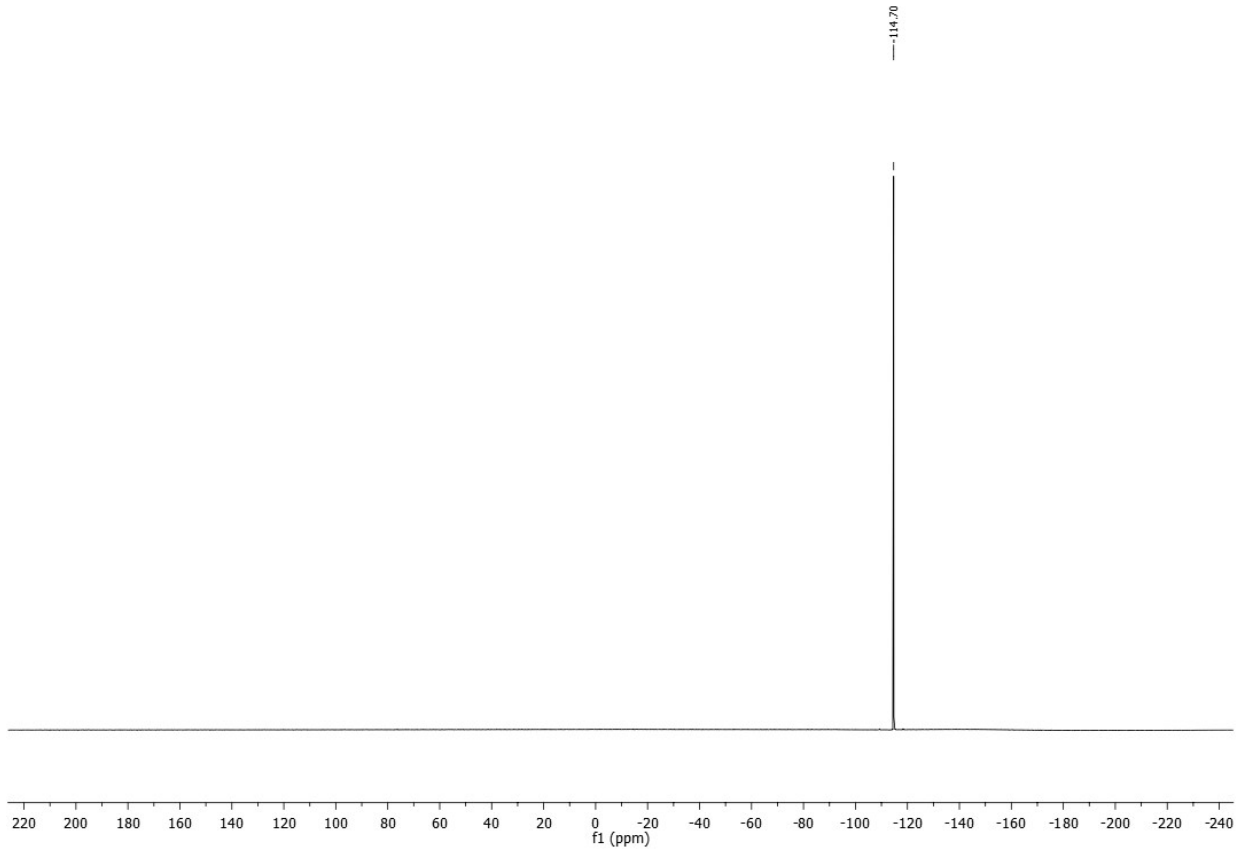


^{1}H NMR and ^{13}C NMR of compound (**4k**)

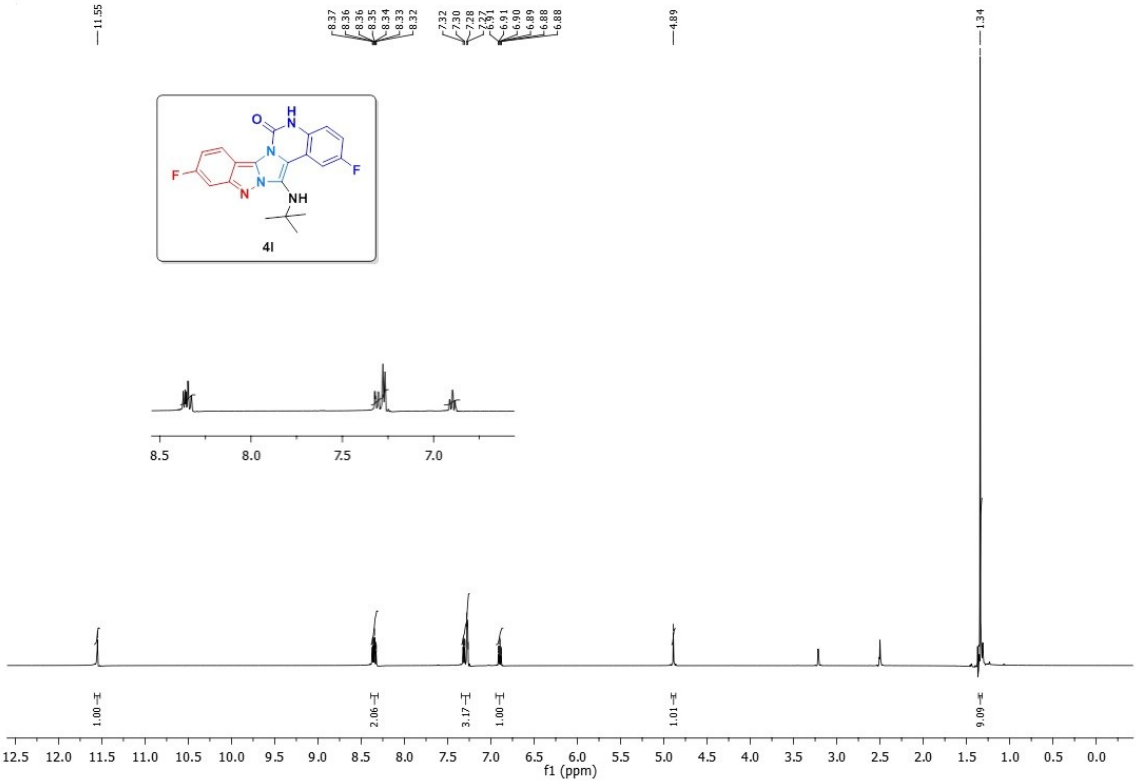


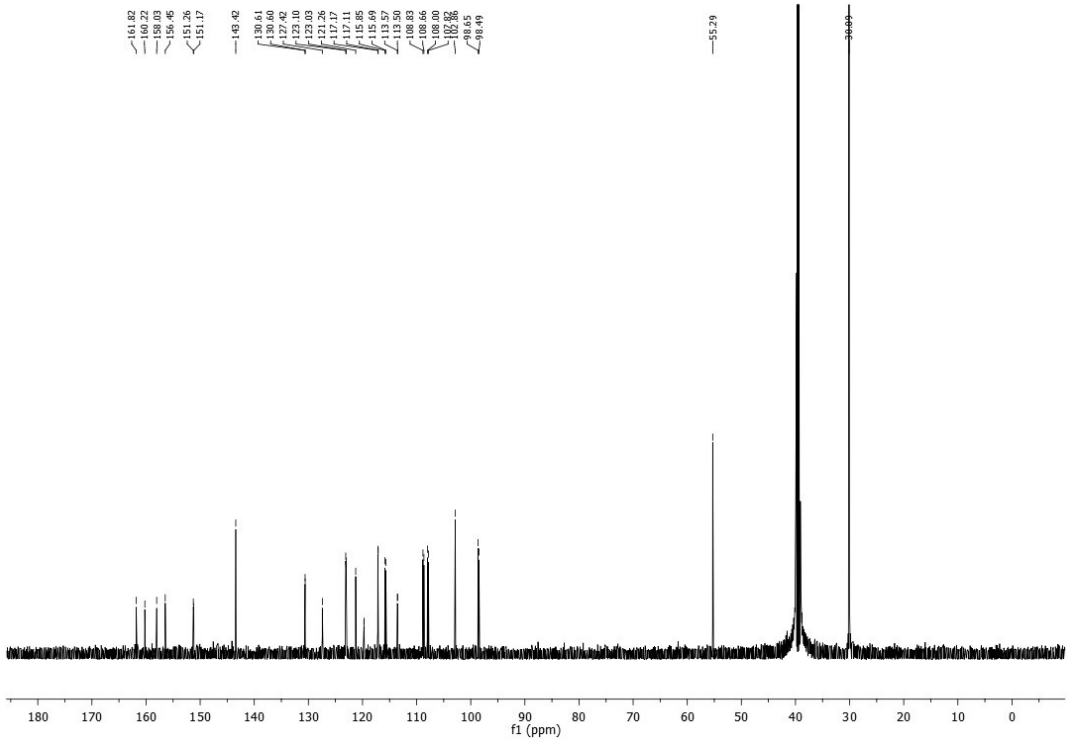


^{19}F NMR of compound (**4k**)

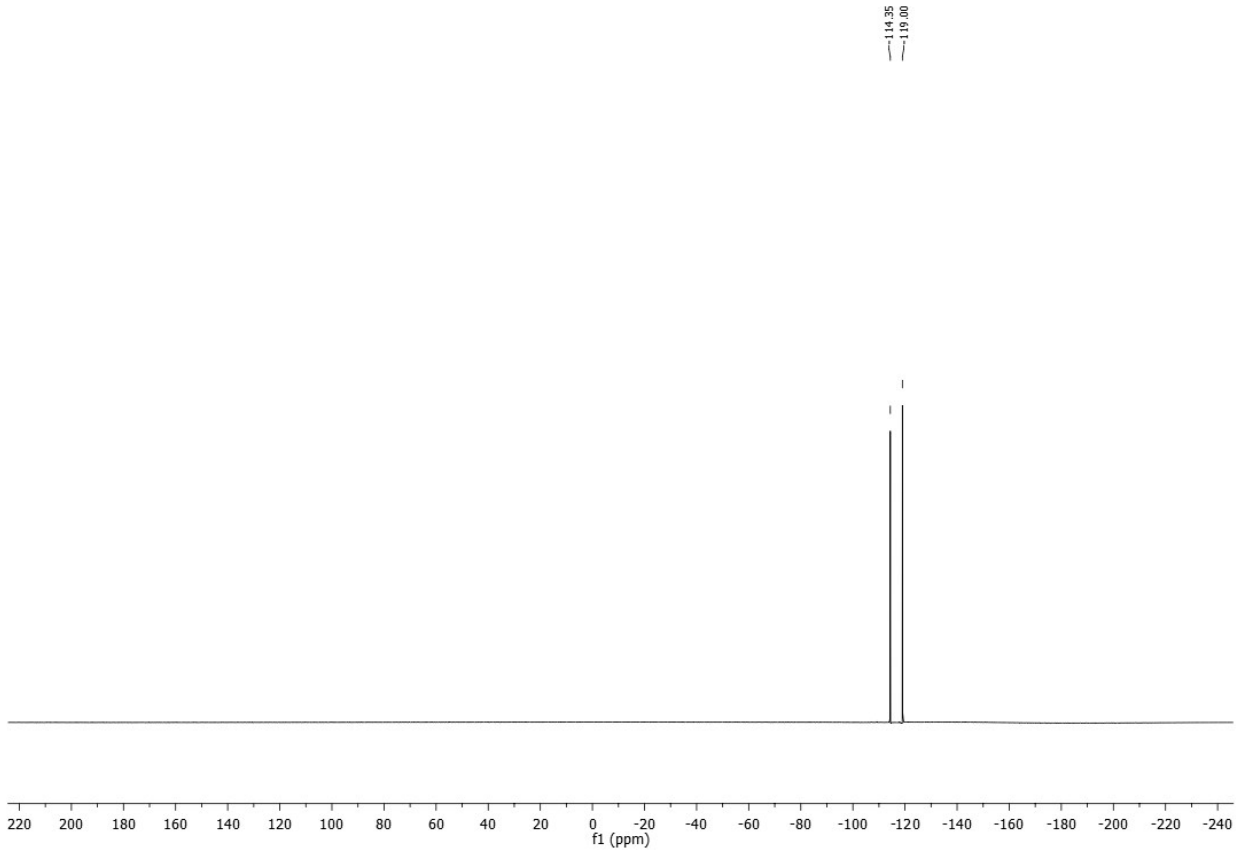


^{1}H NMR and ^{13}C NMR of compound (**4l**)

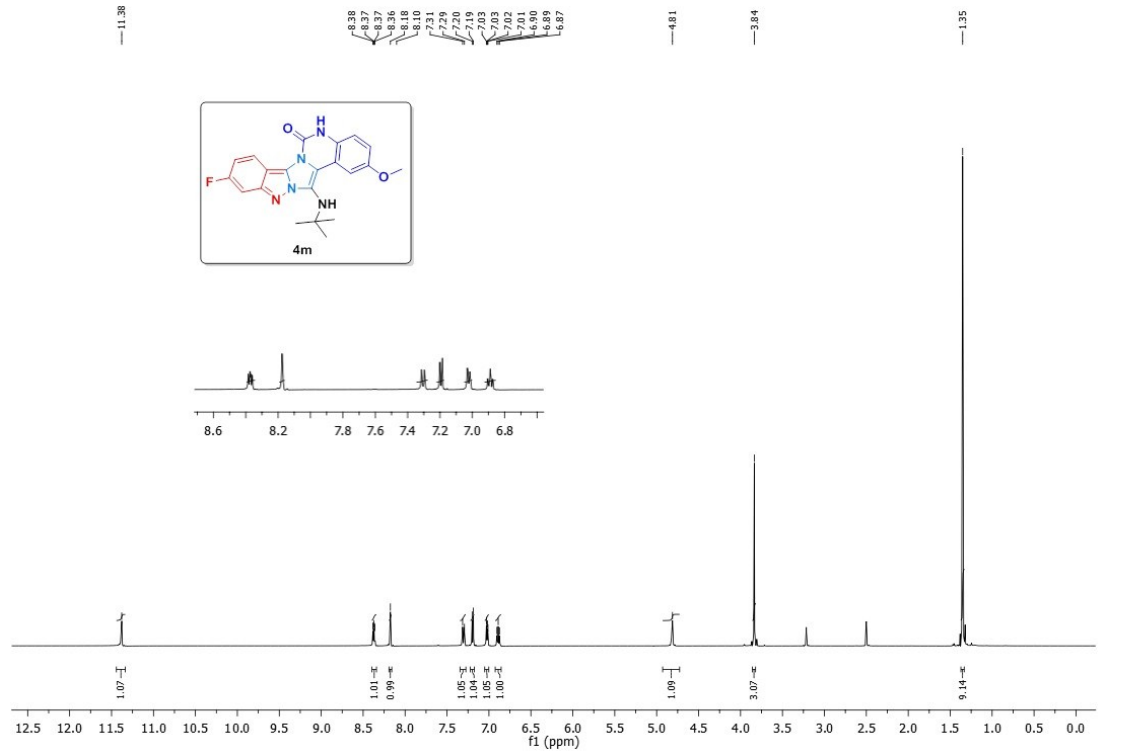


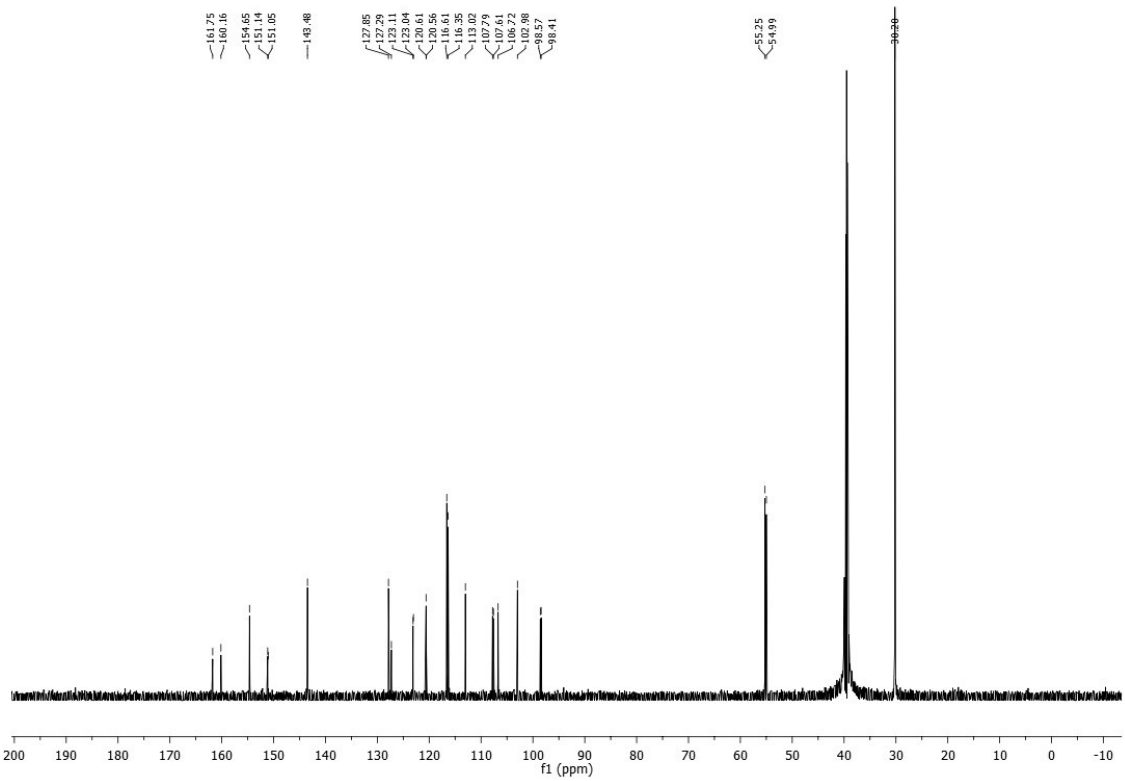


^{19}F NMR of compound (**4l**)

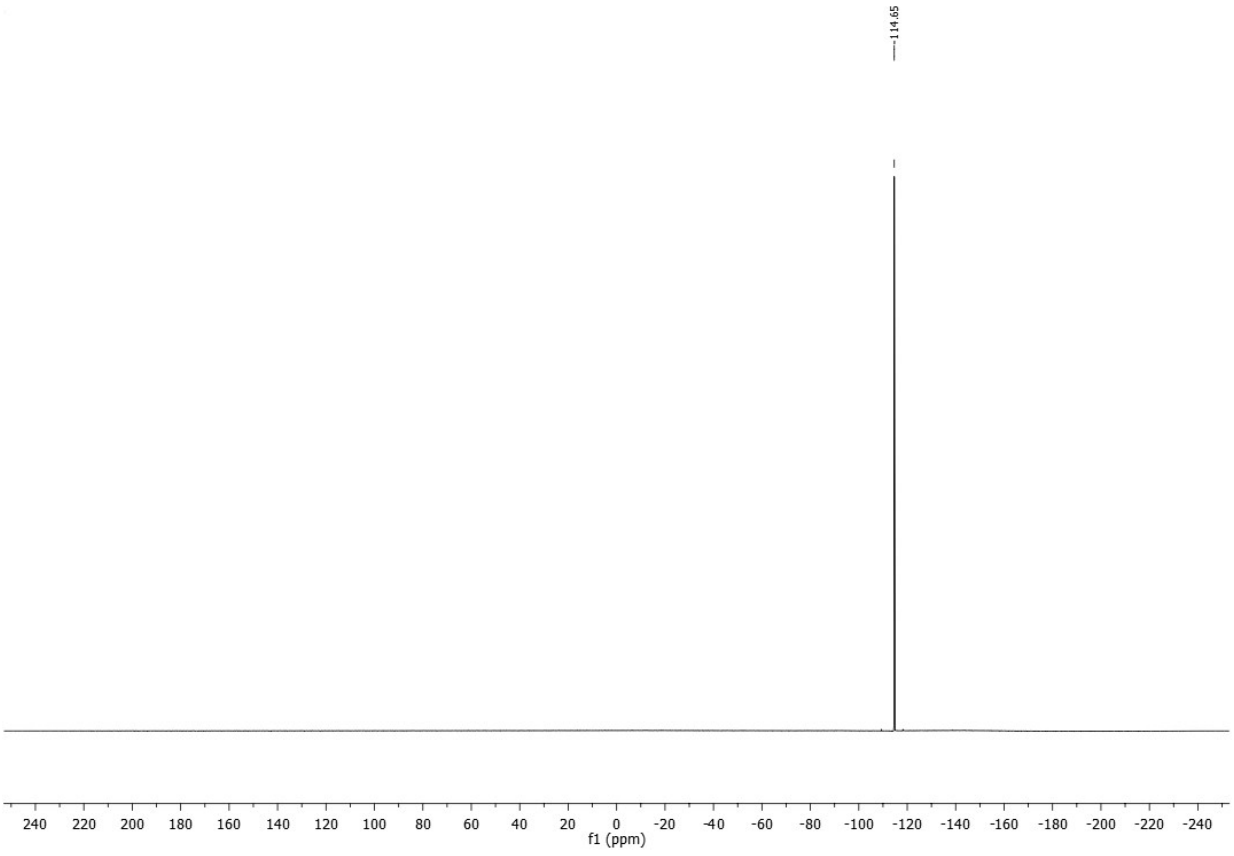


^{1}H NMR and ^{13}C NMR of compound (**4m**)

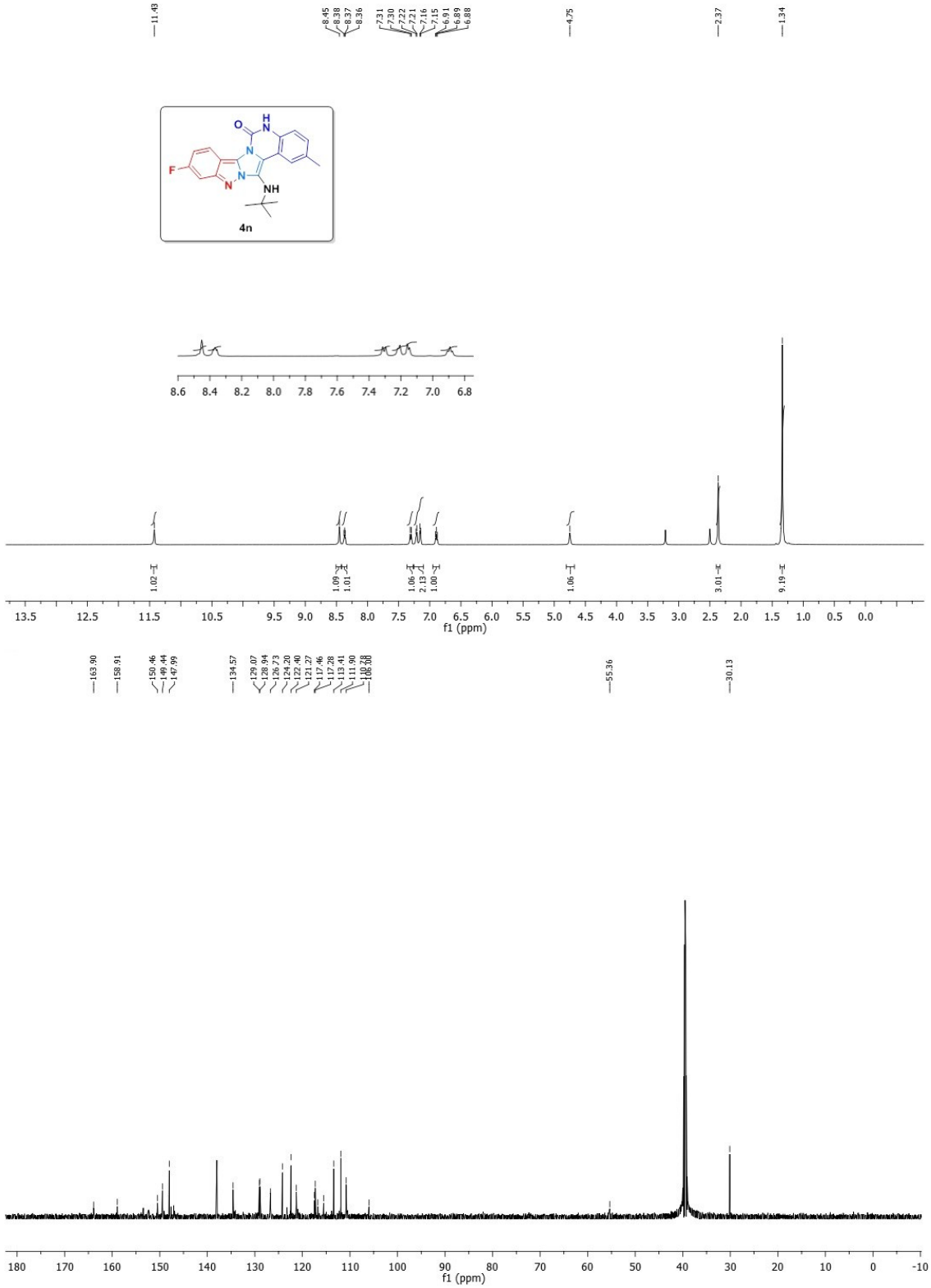




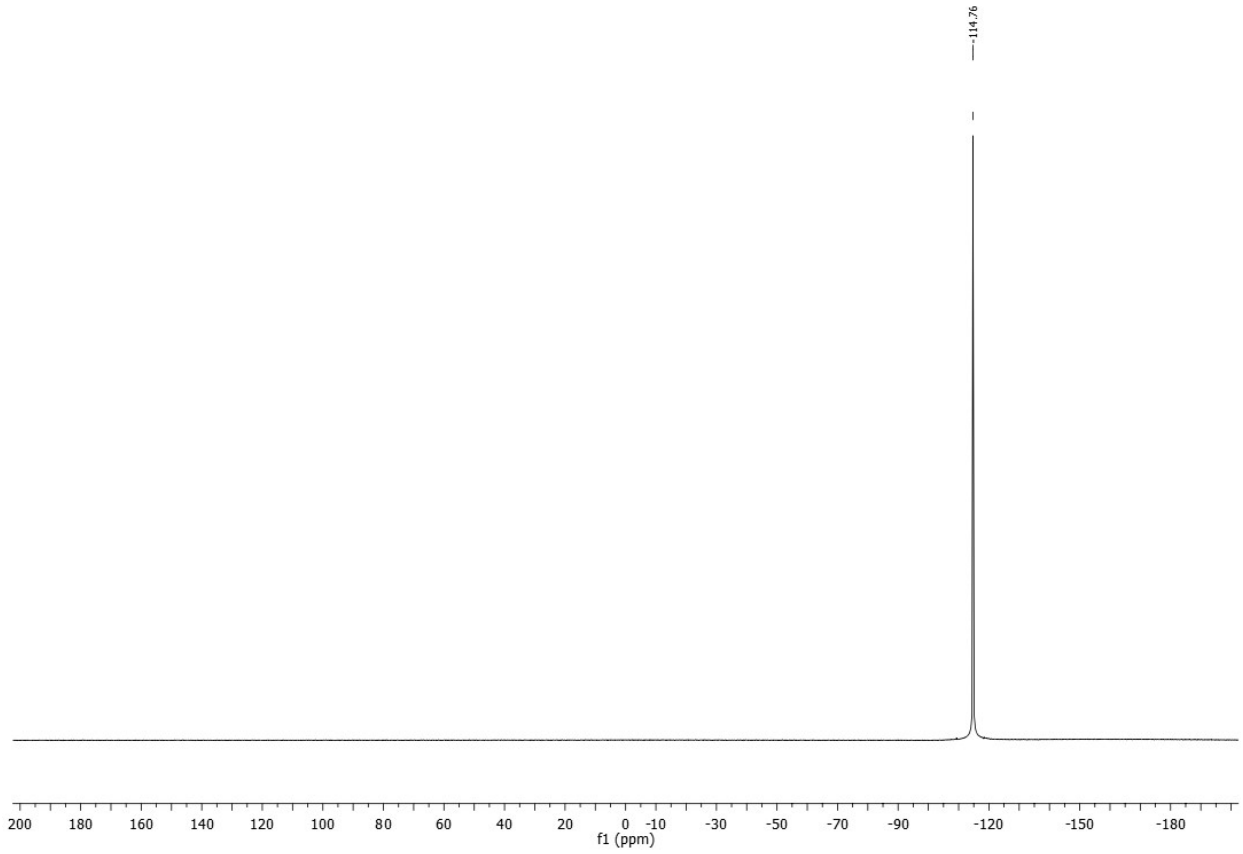
^{19}F NMR of compound (**4m**)



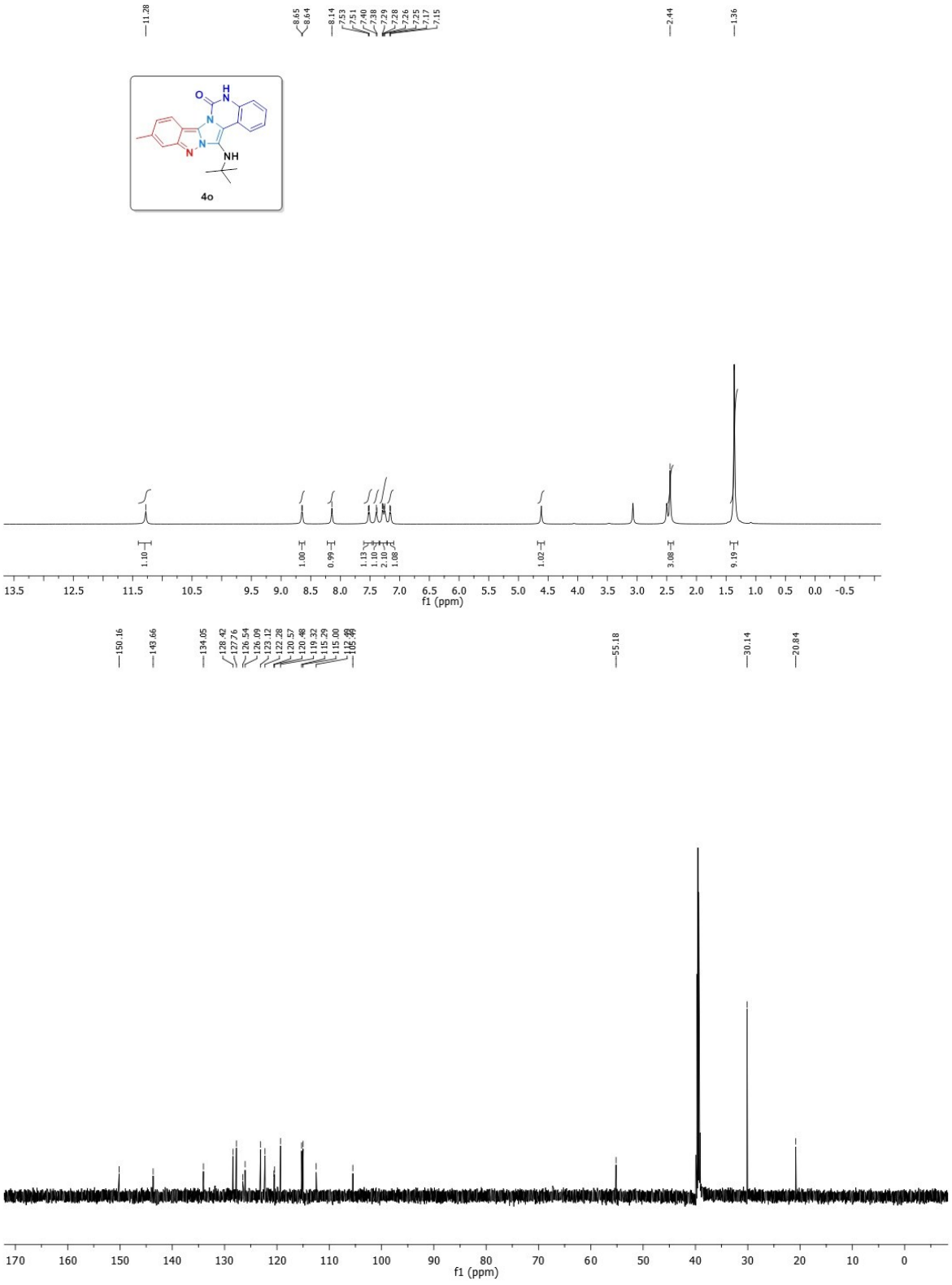
^{1}H NMR and ^{13}C NMR of compound (**4n**)



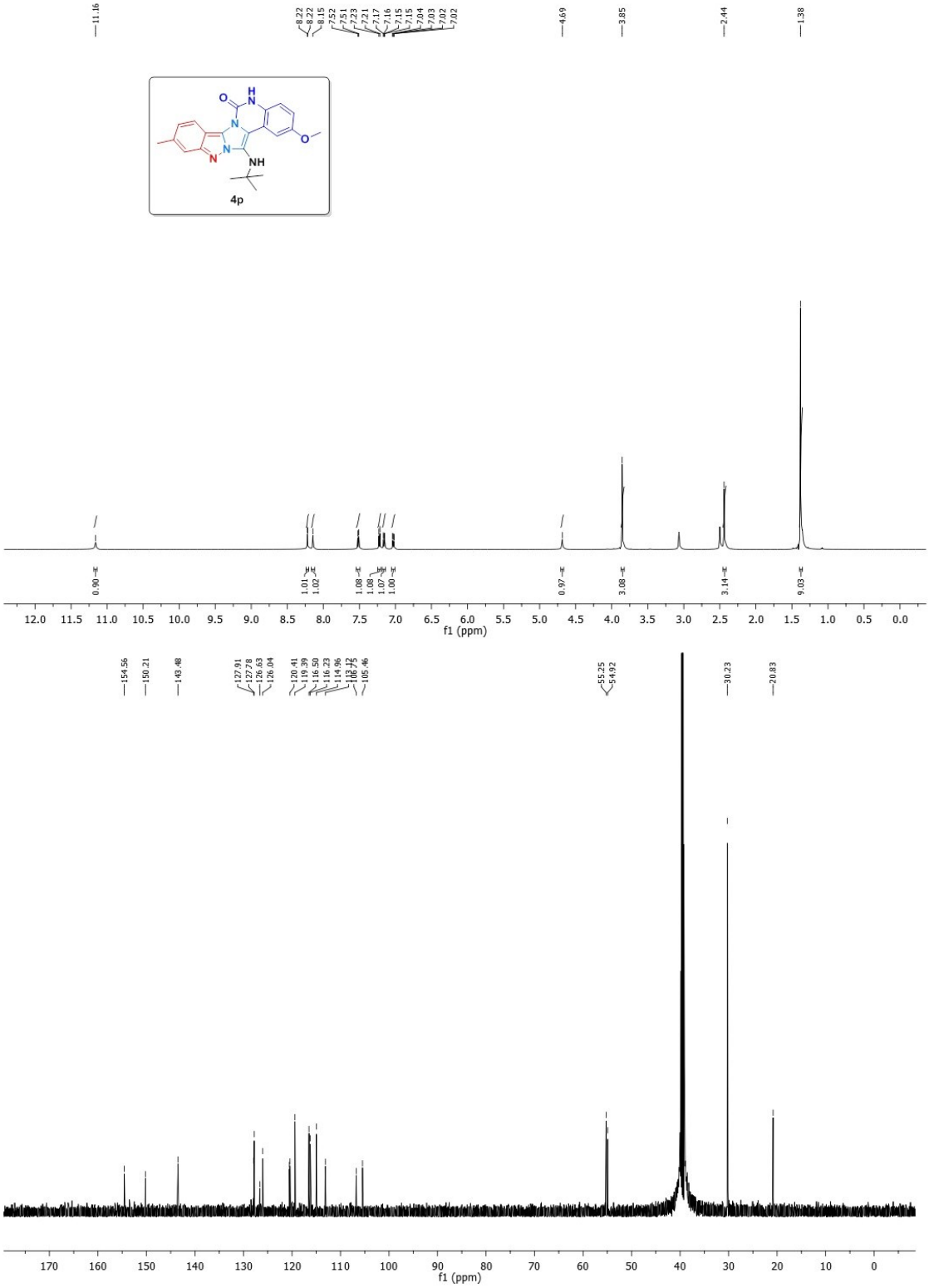
^{19}F NMR of compound (**4n**)



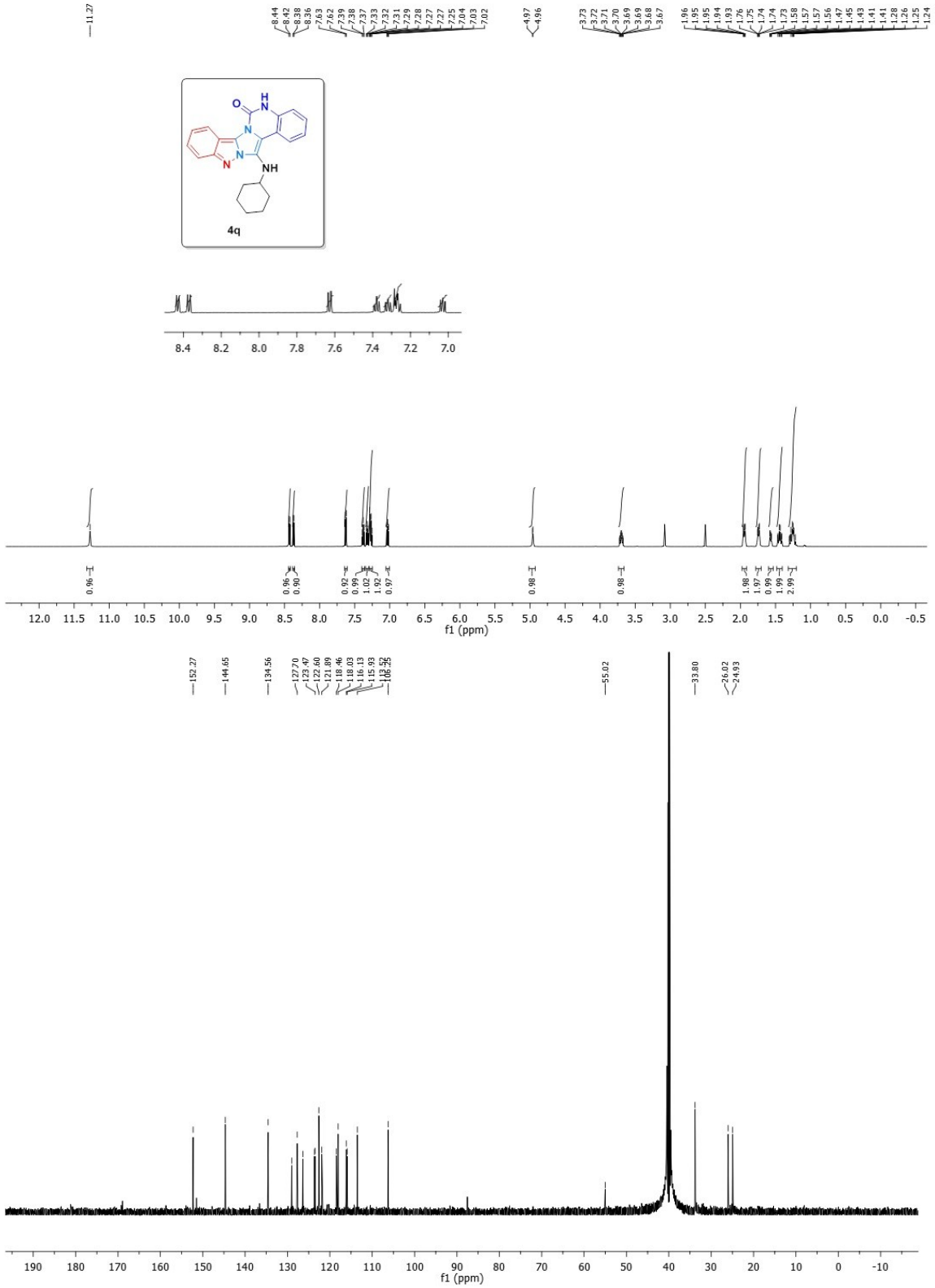
^{1}H NMR and ^{13}C NMR of compound (**4o**)



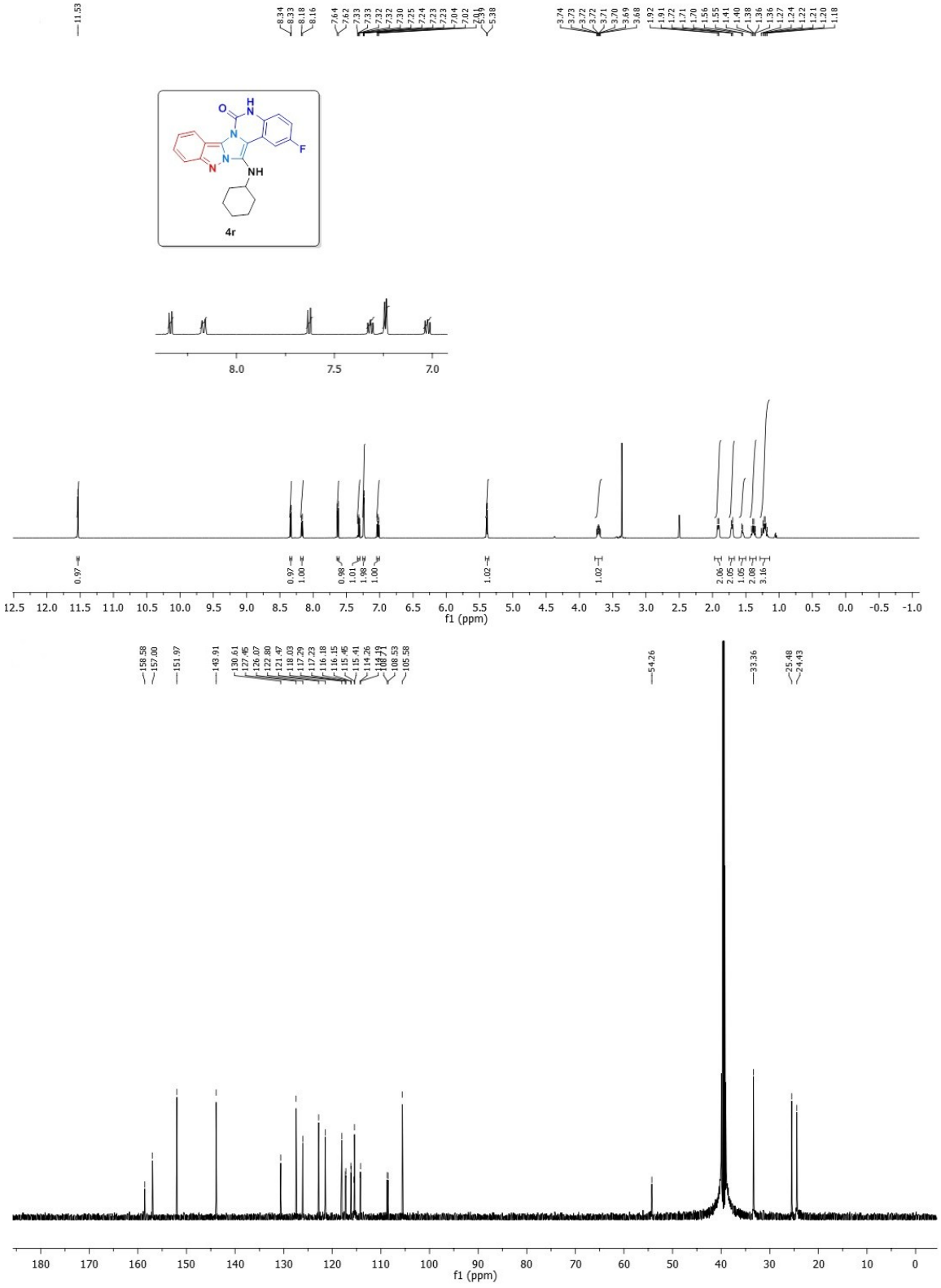
^{1}H NMR and ^{13}C NMR of compound (**4p**)



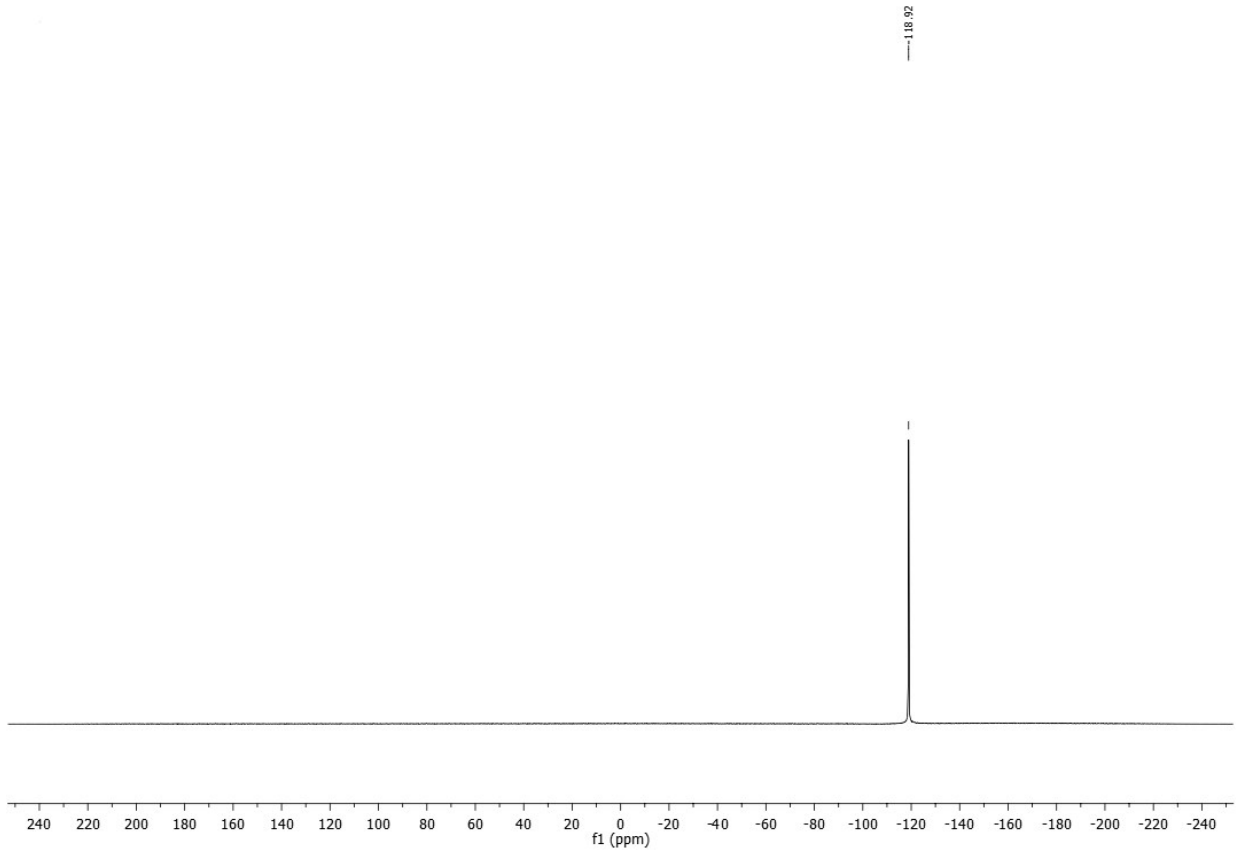
^{1}H NMR and ^{13}C NMR of compound (**4q**)



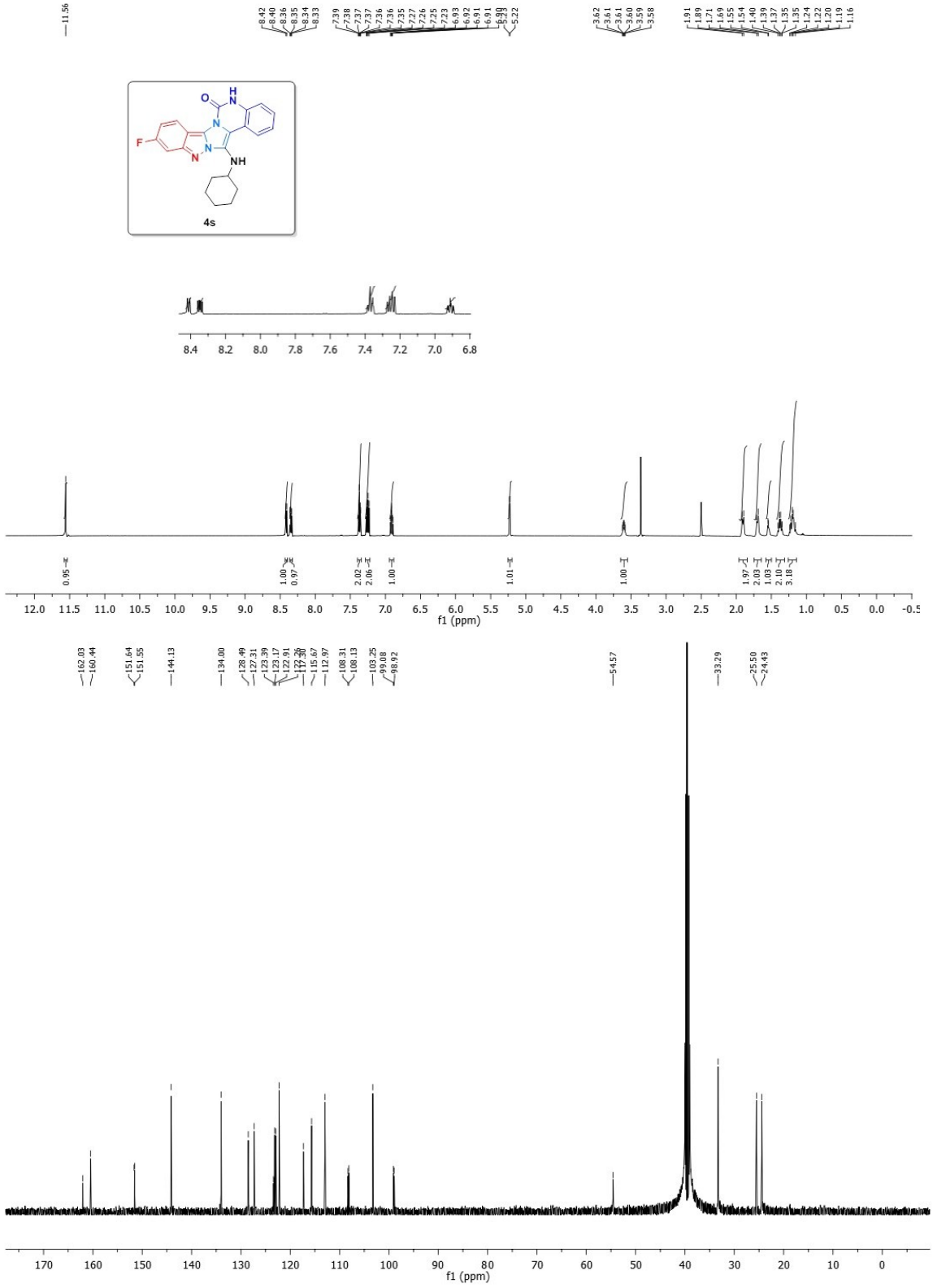
^{1}H NMR and ^{13}C NMR of compound (**4r**)



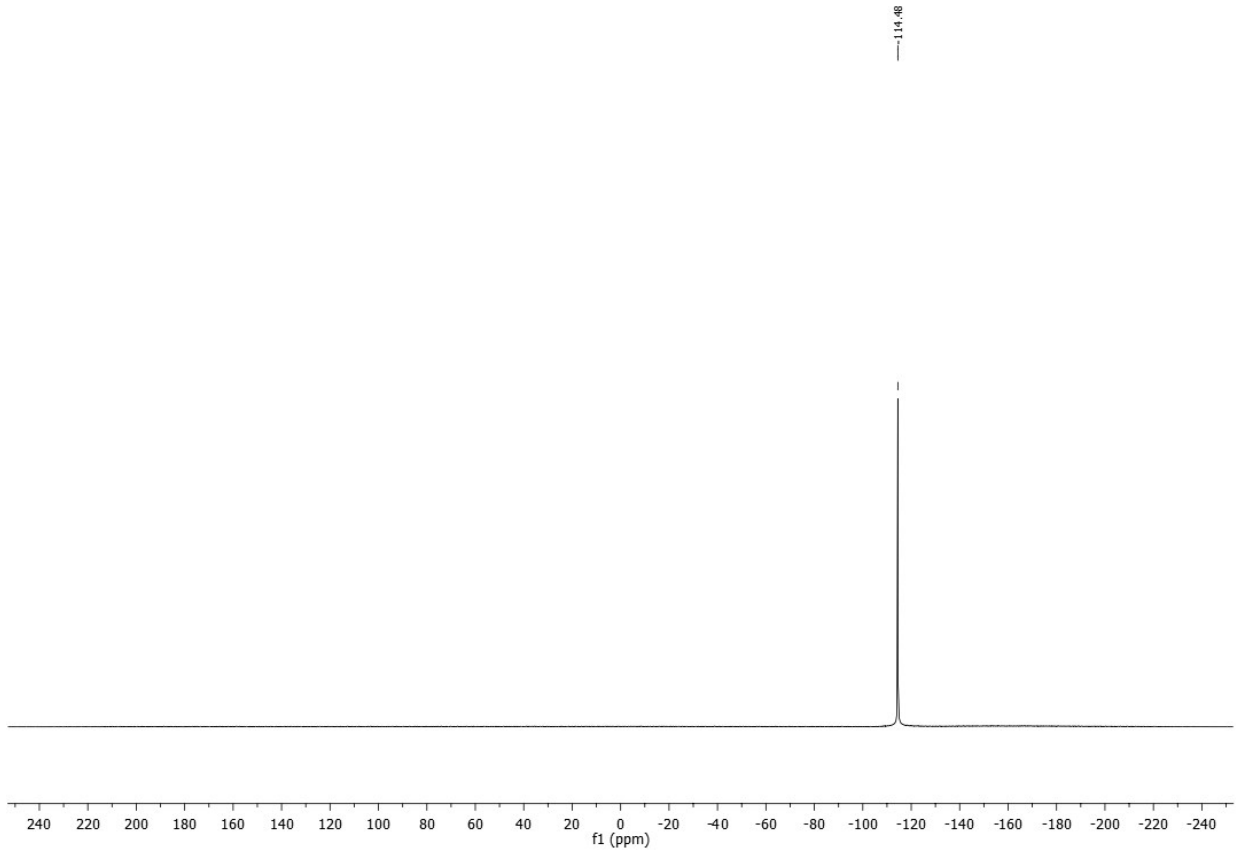
^{19}F NMR of compound (**4r**)



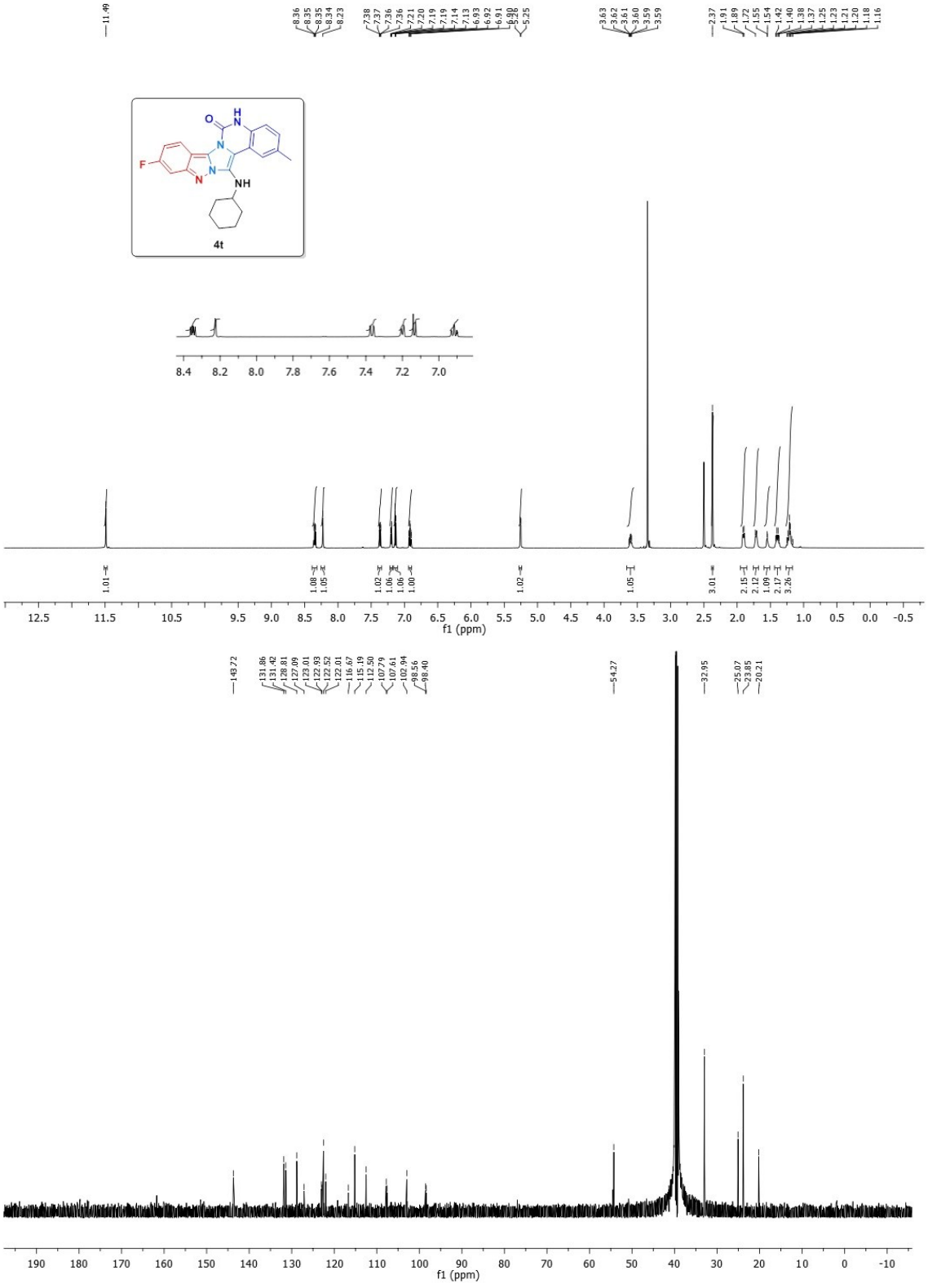
^{1}H NMR and ^{13}C NMR of compound (**4s**)



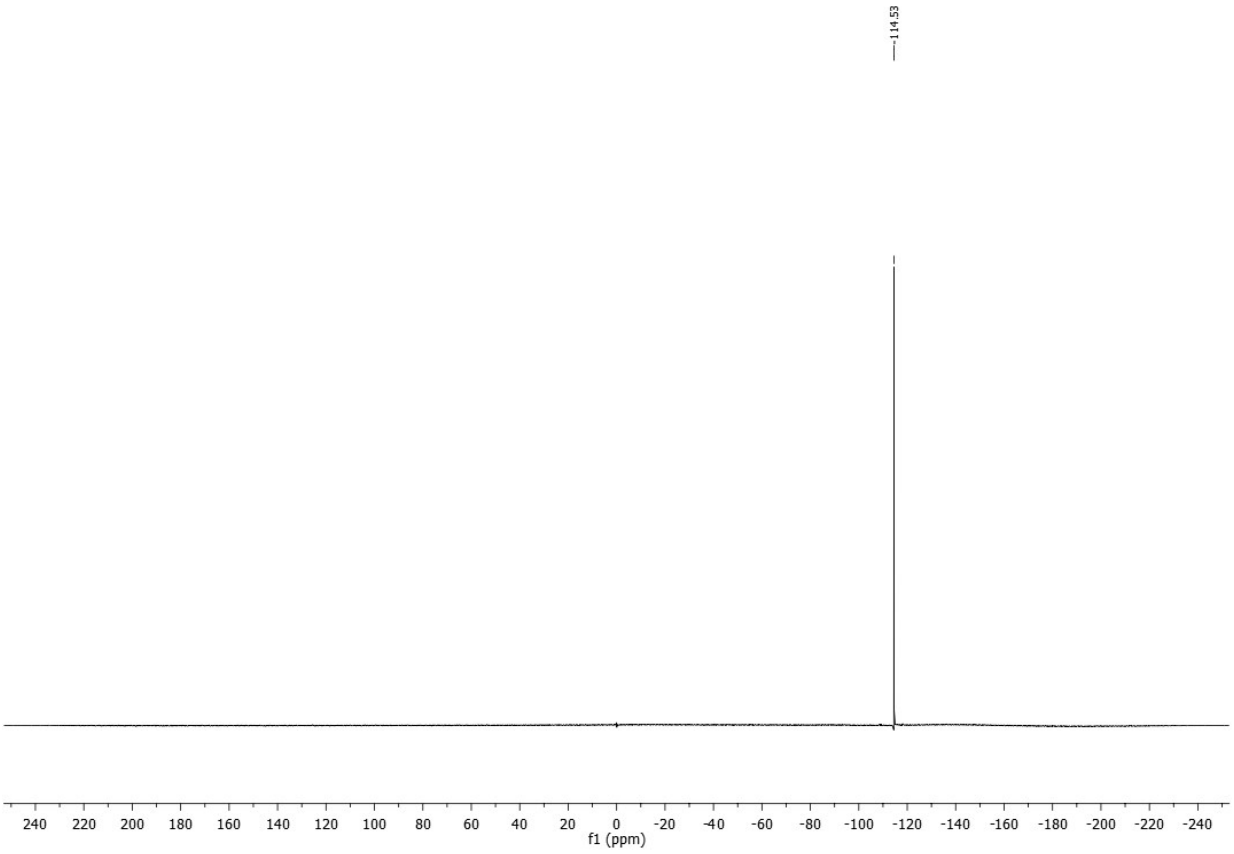
^{19}F NMR of compound (**4s**)



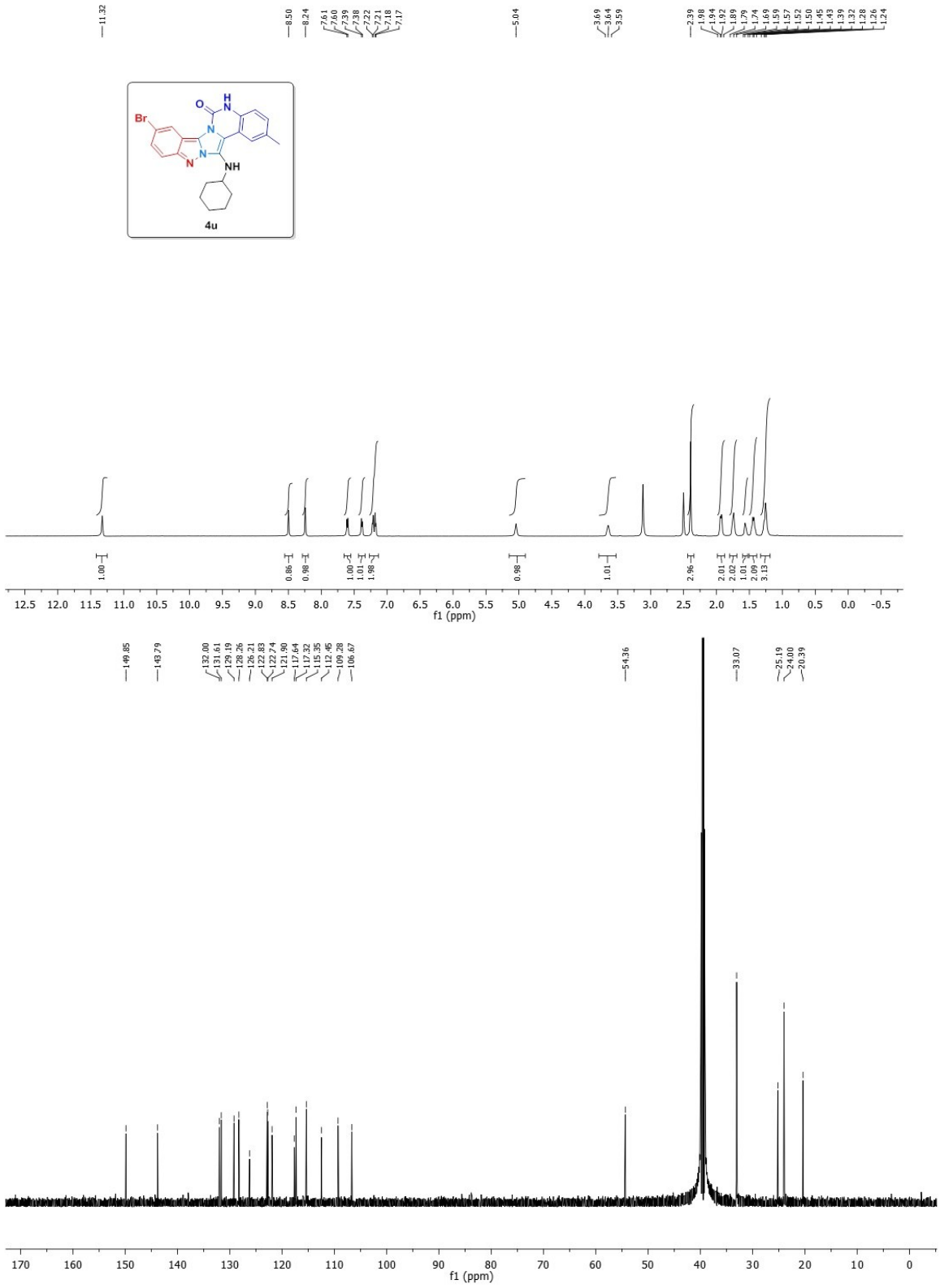
^{1}H NMR and ^{13}C NMR of compound (**4t**)



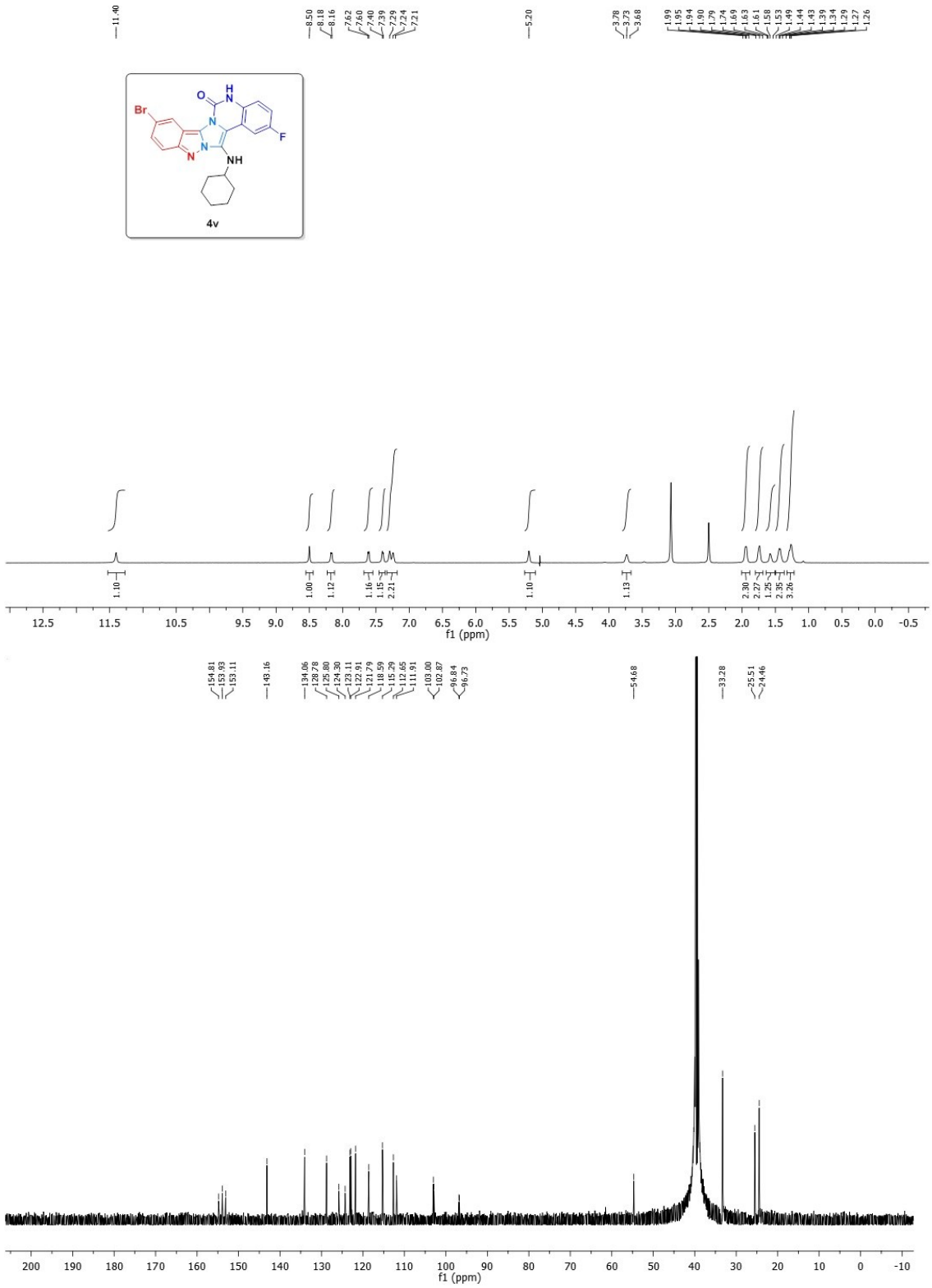
^{19}F NMR of compound (**4t**)



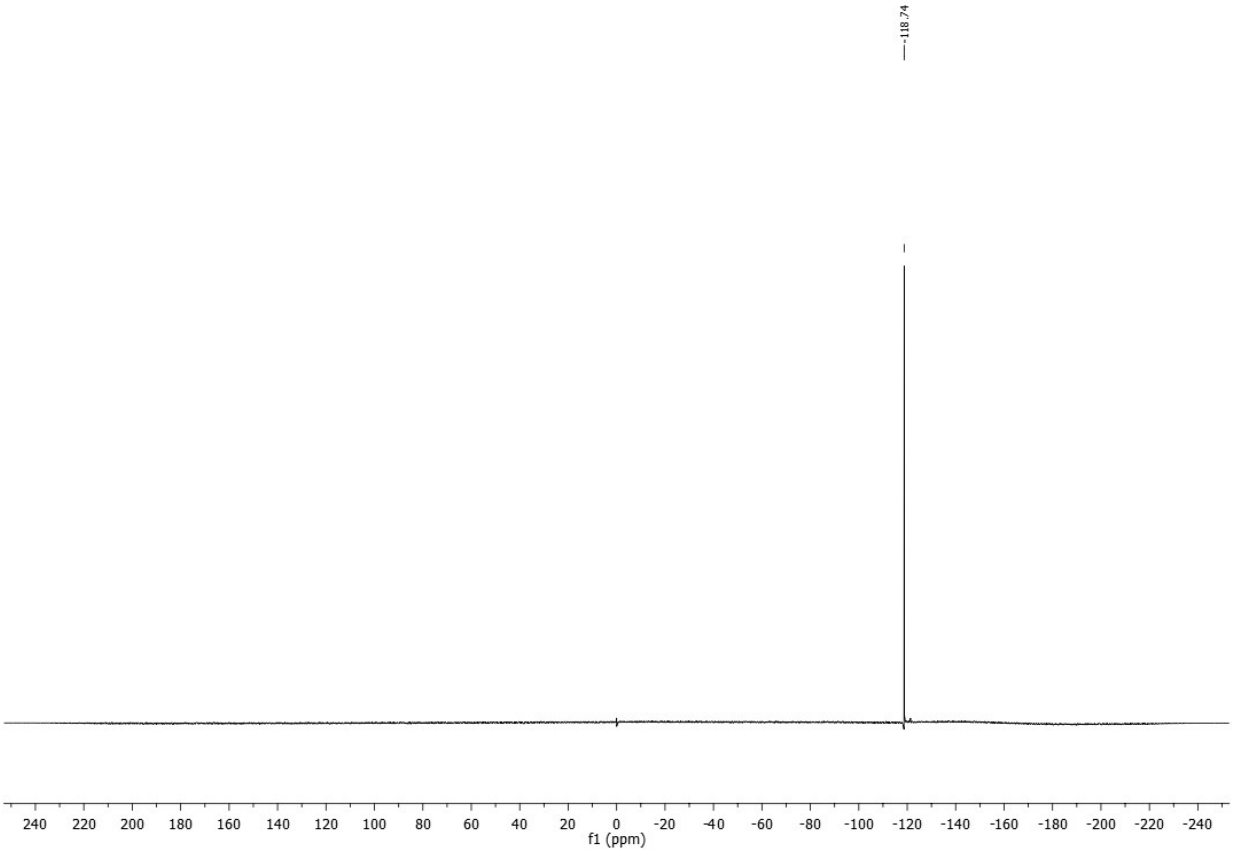
^{1}H NMR and ^{13}C NMR of compound (**4u**)



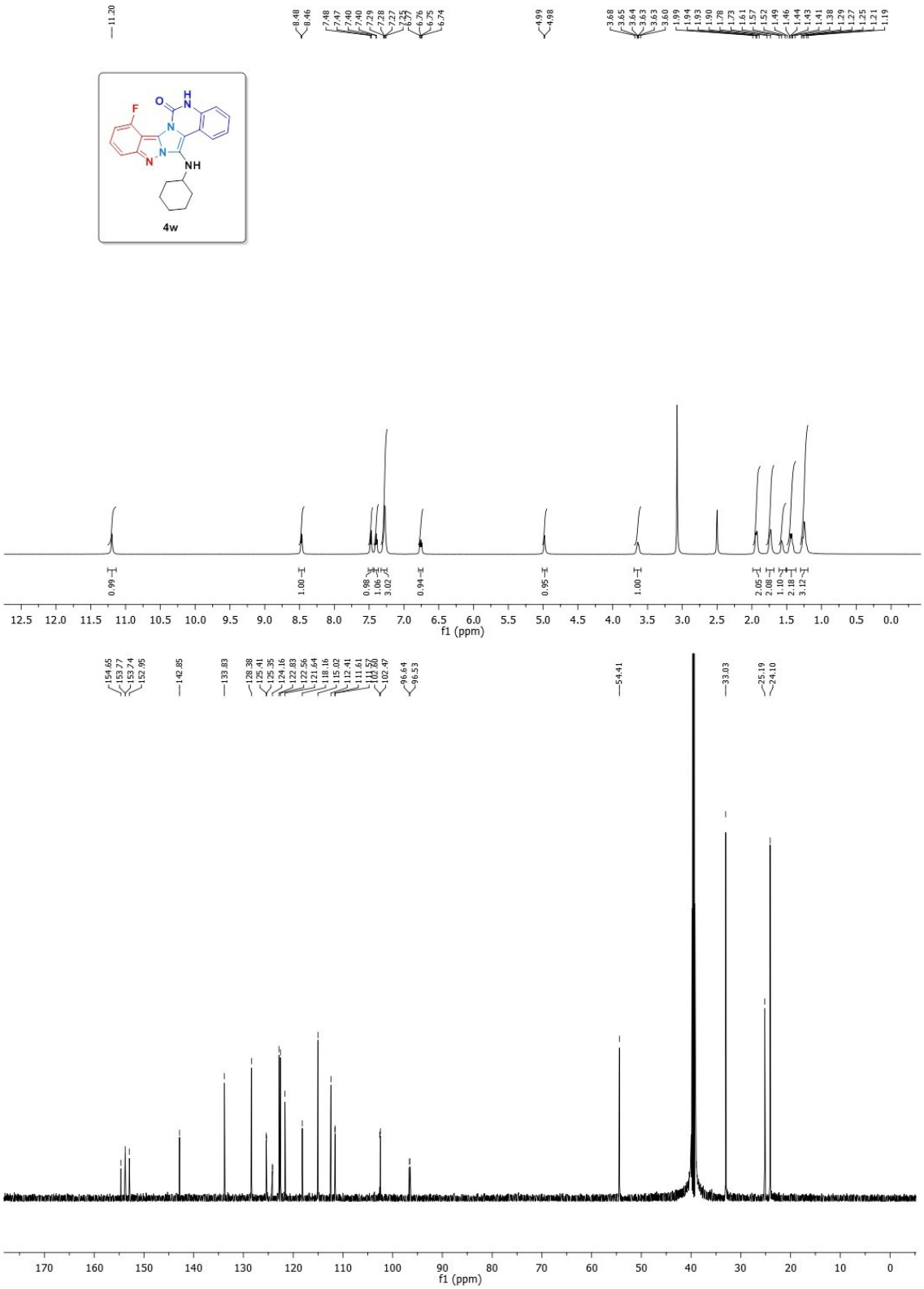
^{1}H NMR and ^{13}C NMR of compound (**4v**)



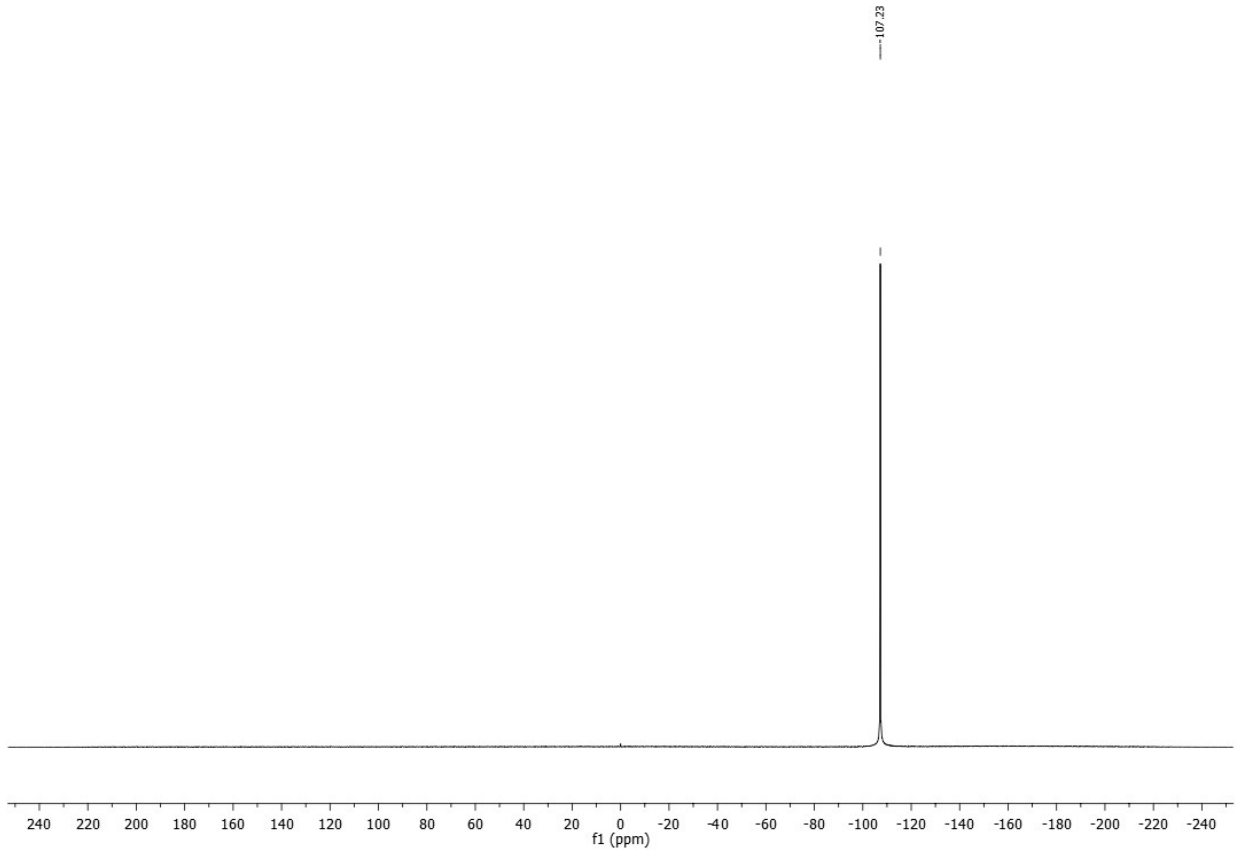
^{19}F NMR of compound (**4v**)



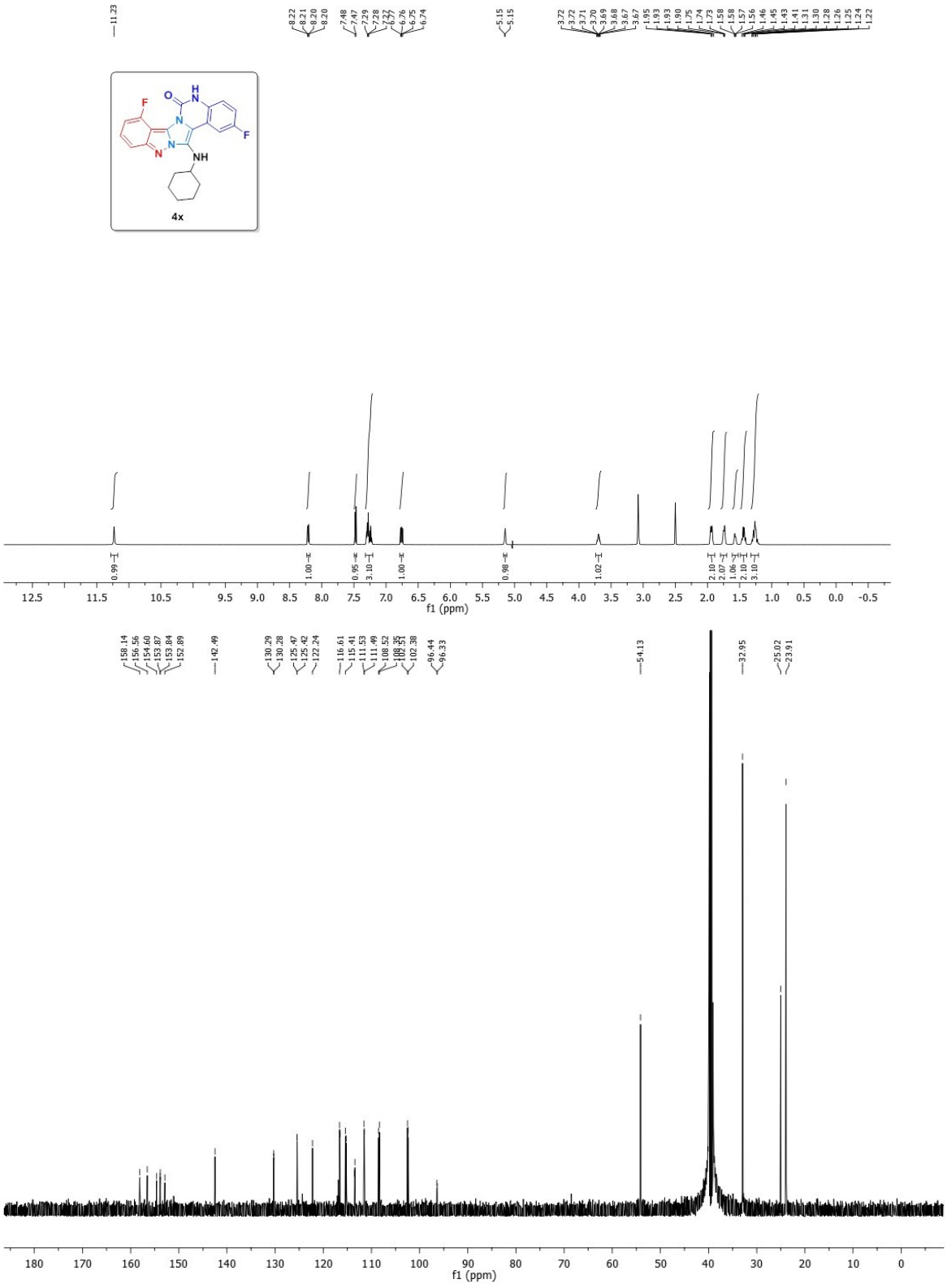
^{1}H NMR and ^{13}C NMR of compound (**4w**)



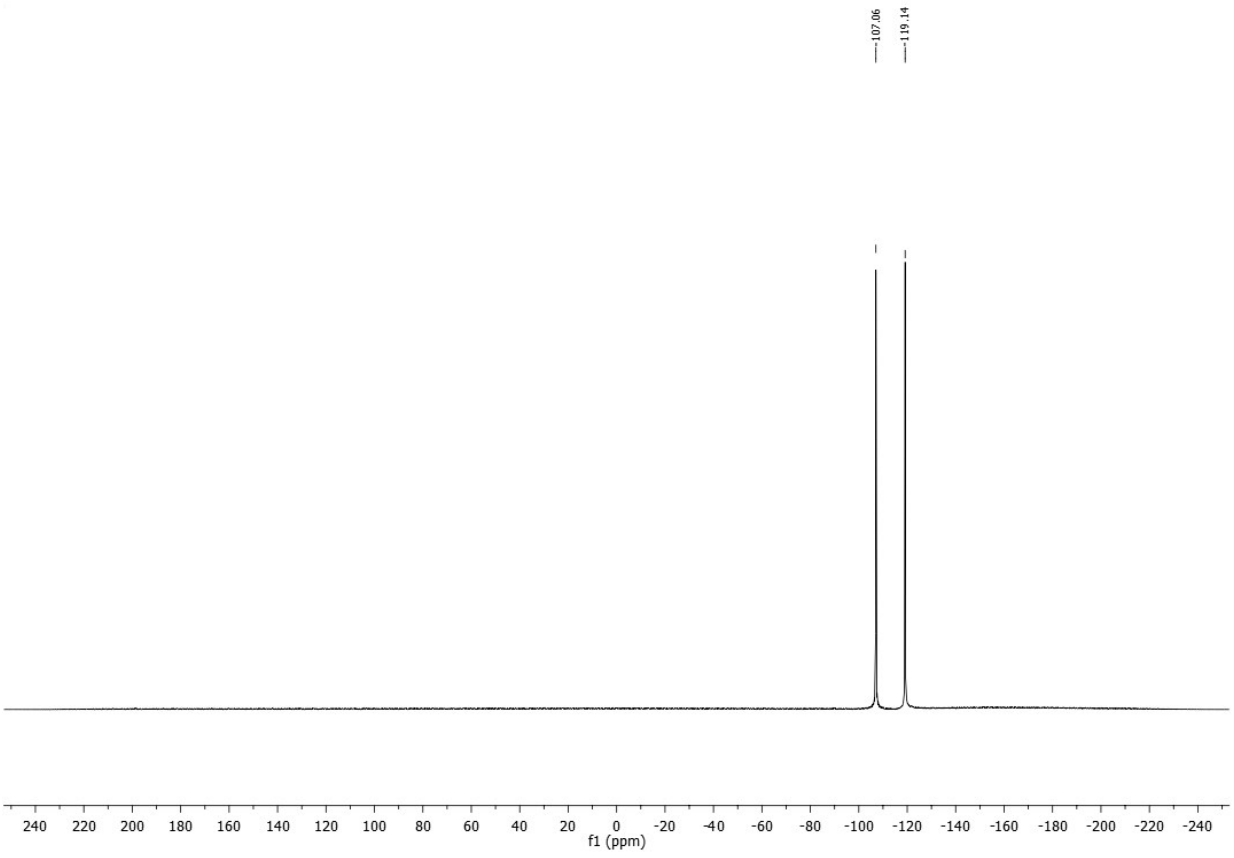
^{19}F NMR of compound (**4w**)



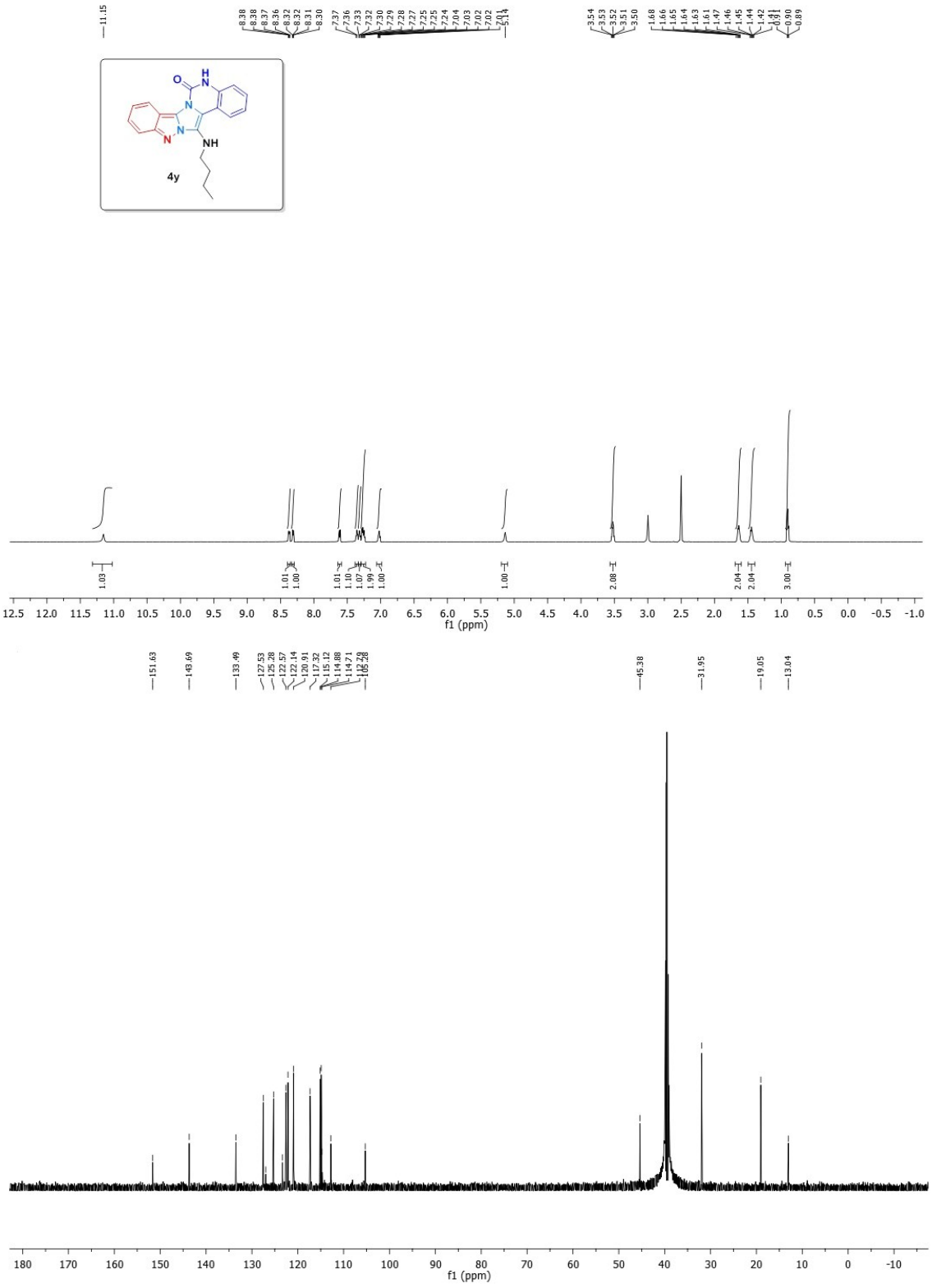
^{1}H NMR and ^{13}C NMR of compound (**4x**)



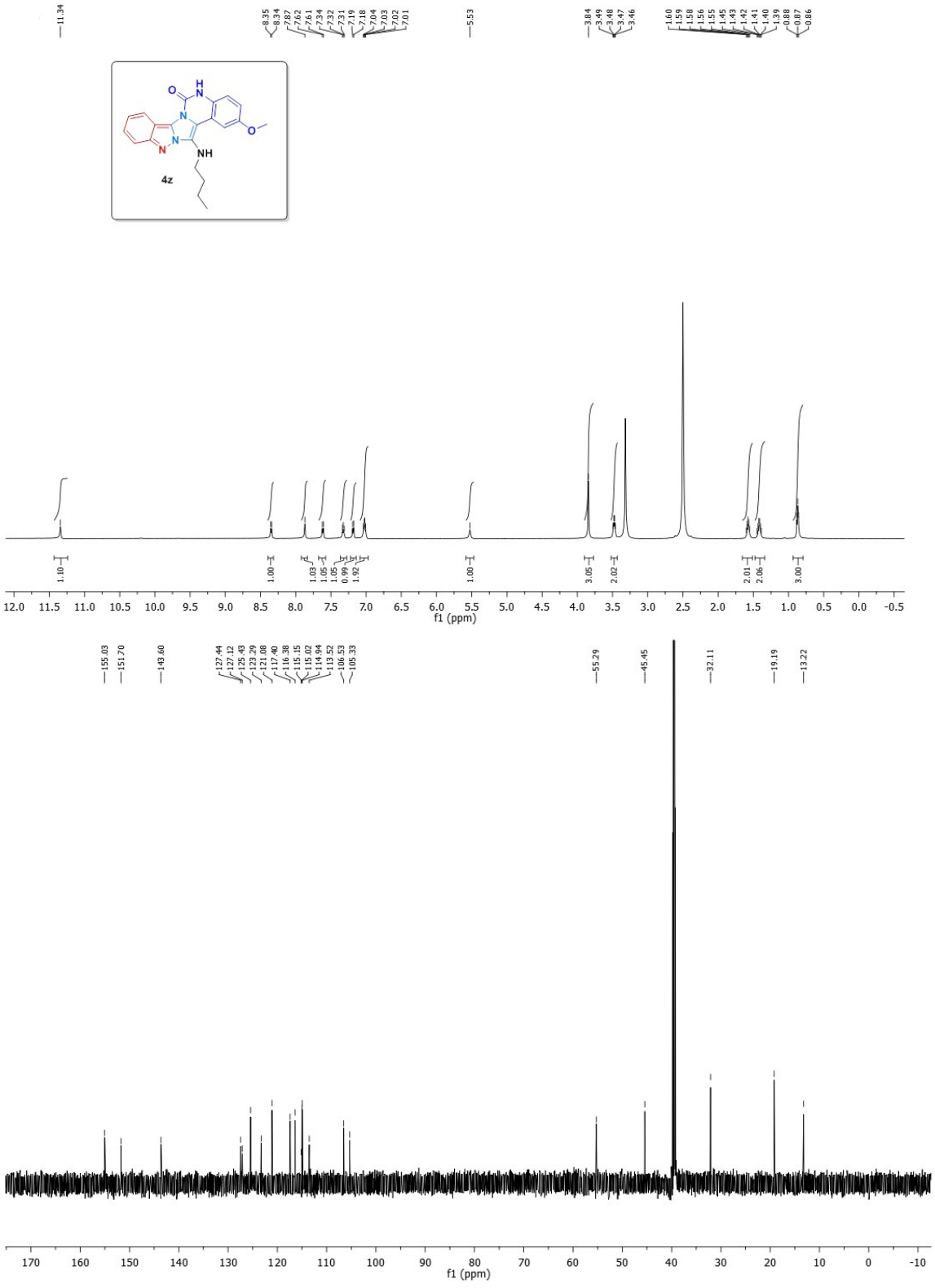
^{19}F NMR of compound (**4x**)



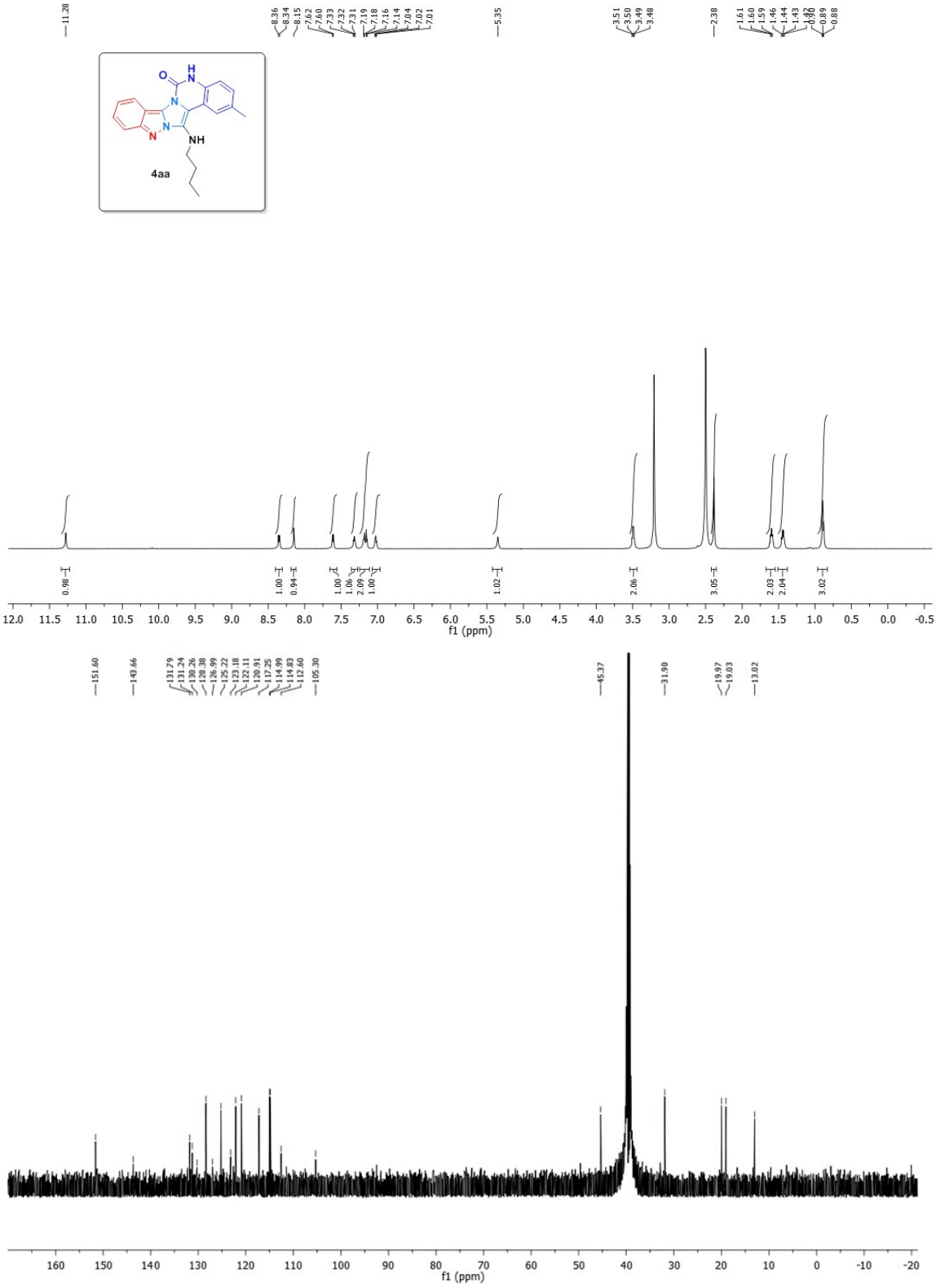
^{1}H NMR and ^{13}C NMR of compound (**4y**)



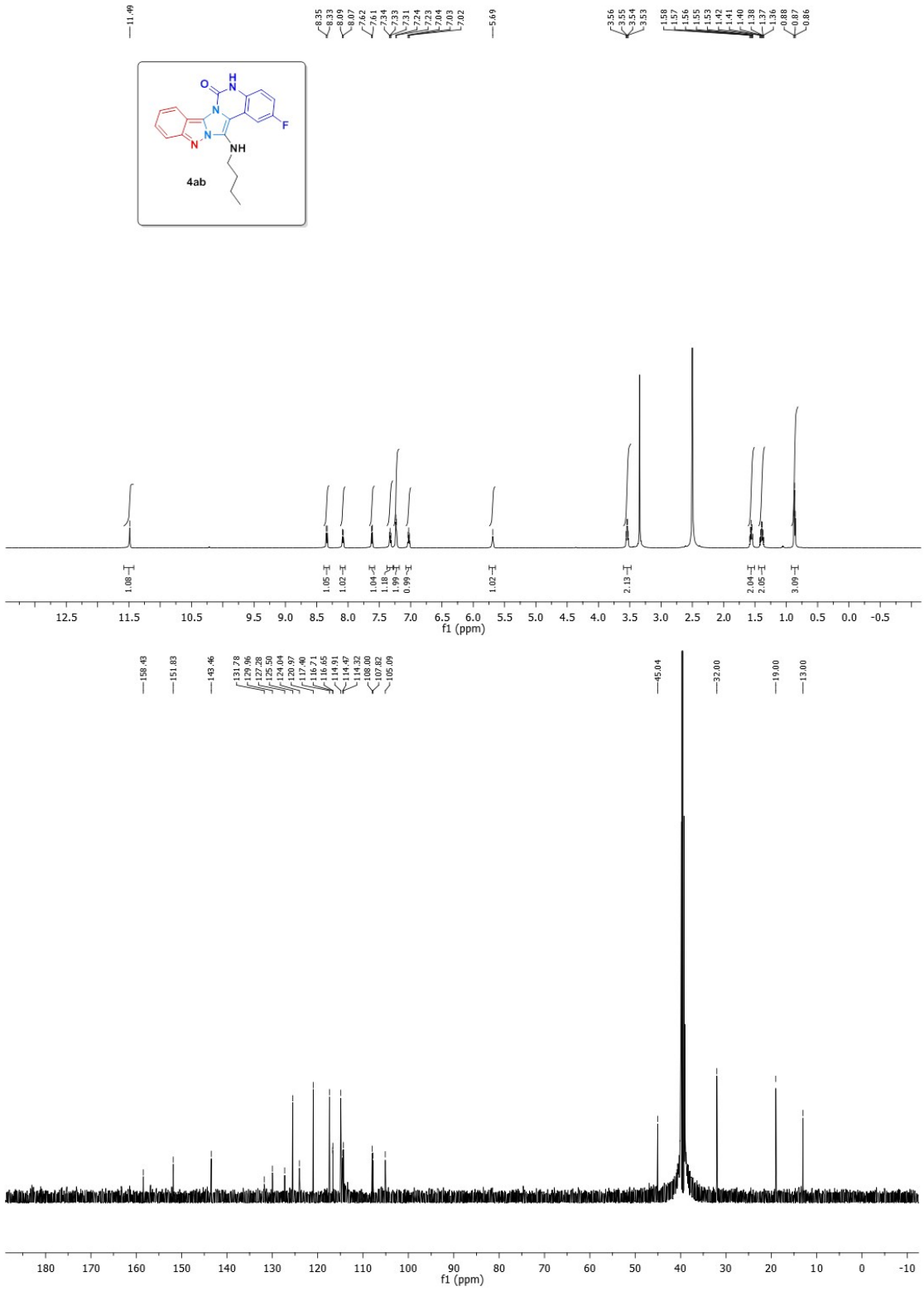
^{1}H NMR and ^{13}C NMR of compound (**4z**)



^{1}H NMR and ^{13}C NMR of compound (**4aa**)



^{1}H NMR and ^{13}C NMR of compound (**4ab**)



^{1}H NMR and ^{13}C NMR of compound (**4ac**)